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(54) Title: ENHANCED SURVIVAL OF CANCER PATIENTS TREATED WITH ERYTHROPOIETIN AND ANTITUMOR AGENTS

(57) Abstract

The present invention provides a method to treat anemic and non-anemic subjects having malignancies who receive non-platinum and platinum containing chemotherapy such that there is a reduced need for transfusion and a greater hemoglobin level after chemotherapeutic treatment. The present invention provides a method to treat anemic and non-anemic subjects having malignancies who receive non-platinum and platinum containing chemotherapy such that anemia may be successfully prevented or treated during the course of a chemotherapeutic regimen. The present invention provides a method to treat anemic and non-anemic subjects having malignancies who receive non-platinum and platinum containing chemotherapy such that the patients show greater quality of life, and show improvement in physical performance and well being. The present invention provides a method to treat anemic and non-anemic subjects having malignancies who receive non-platinum and platinum containing chemotherapy such that the overall survival rate after two years is increased compared to a treatment with a chemotherapeutic agent alone. The present invention provides algorithms for prediction of early response to erythropoietin therapy related to changes in ferritin, hemoglobin and transferrin receptor levels for subjects who receive non-platinum and platinum containing chemotherapy.

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ENHANCED SURVIVAL OF CANCER PATIENTS TREATED WITH ERYTHROPOIETIN AND ANTITUMOR AGENTS

CROSS-REFERENCE TO RELATED APPLICATION

This application claims priority from United States provisional application Serial No. 60/133418, filed May 11, 1999.

BACKGROUND OF THE INVENTION

Erythropoietin (EPO) is a glycoprotein hormone produced by the kidney in response to tissue hypoxia that stimulates red blood cell production in the bone marrow. The gene for erythropoietin has been cloned and expressed in Chinese hamster ovary (CHO) cells as described in United States Patent No. 4,703,008. Recombinant human erythropoietin (r-HuEPO, Epoetin alfa) has an amino acid sequence identical to that of human urinary erythropoietin, and the two are indistinguishable in chemical, physical and immunological tests. Recombinant human erythropoietin acts by increasing the number of cells capable of differentiating into mature erythrocytes, triggering their differentiation and augmenting hemoglobin synthesis in developing erythroblasts (Krantz SB. *Blood* (1991) 77: 419-434, Beckman BS, Mason-Garcia M. *The Faseb Journal* (1991) 5: 2958-2964).

Studies were conducted in various animal models to characterize the potential toxic effects of Epoetin alfa on systemic function following acute and chronic administration, the mutagenic and antigenic potential of Epoetin alfa as well as its effect on reproductive capabilities. Based on the results of these preclinical trials, the benefit of Epoetin alfa to ameliorate anemia is considered to outweigh by far any adverse reaction in adults within the proposed clinical dose range of 50-500 IU/kg three times per week. Epoetin alfa has been administered in healthy volunteers over a dose range of 100-300 IU/kg by the SC and IV routes. When given SC, single doses of 50 or 100 IU/kg SC were slowly absorbed from the injection site, reaching a peak between 12 and 18 hours post dosing. The half-life is difficult to evaluate for the subcutaneous route and is estimated about 24 hours, as opposed to around 5 hours following intravenous administration. It

can be estimated that the bioavailability of the intact hormone from subcutaneous dosing is about 20 percent.

Although the kidney, liver and bone marrow have been implicated in the metabolism of endogenous EPO and Epoetin alfa in animals, the data are inconclusive. Erythropoietin is heavily glycosylated, which protects the molecule from rapid degradation *in vivo*. In both animal and human studies, urinary excretion of intact erythropoietin contributes about 3 to 10% of its total clearance. Pharmacokinetic data of studies in cancer patients indicate that the pharmacokinetics of exogenously administered Epoetin alfa is not remarkably altered in these patients.

In clinical trials to date, Epoetin alfa has been evaluated in normal subjects as well as in subjects with various anemic conditions. Epoetin alfa induces a brisk haematological response in normal human volunteers, provided that adequate supplies of iron are available to support increased hemoglobin synthesis. A majority of trials have investigated the safety and effectiveness of Epoetin alfa in the treatment of chronic renal failure and of anemia in cancer. Other trials have evaluated Epoetin alfa for the treatment of anemia associated with rheumatoid arthritis, prematurity, AIDS, bone marrow transplantation, myelofibrosis, sickle cell anemia, as a facilitator of presurgical autologous blood donation, and as a perisurgical adjuvant.

Epoetin alfa has been well tolerated in studies conducted to date. Hypertensive encephalopathy and seizures have occasionally been described in dialysis patients treated with Epoetin alfa, particularly during the early phase of therapy when hematocrit is rising. (Eschbach JW, Egrie JC, Downing MR, Browne JK, Adamson JW. *New Engl J Med* (1987) 316: 73-78, Winearls CG, Oliver DO, Pippard MJ, et al. *Lancet* (1986) 2 (8517): 1175-1177). Such reports became more rare as experience of use of the compound developed. Occasionally, cancer patients treated with Epoetin alfa have experienced an increase in blood pressure associated with a significant increase in hematocrit. The risk, however, appears substantially lower than in chronic renal failure patients.

No antibody titers against Epoetin alfa could be demonstrated and confirmed in subjects treated with Epoetin alfa for up to 2 years, indicating the absence of immunological sensitivity to Epoetin alfa. Skin rashes and urticaria have been observed rarely and when reported have been mild and transient in nature, but suggest allergic hypersensitivity to some components of the Epoetin alfa formulation.

Epoetin alfa is approved for sale in many countries for the treatment of anemia in chronic renal failure (dialysis and predialysis), anemia in zidovudine treated HIV positive patients (US), anemia in cancer patients receiving platinum-based chemotherapy, as a facilitator of autologous blood predonation, and as a perisurgical adjuvant to reduce the likelihood of requiring allogeneic blood transfusions in patients undergoing orthopedic surgery.

Early clinical trials with Epoetin in cancer involved anemic patients with a variety of malignant diseases and have provided information on the effect of Epoetin on the hemoglobin concentrations, hematocrit and subsequent red blood cell transfusion requirements of such patients. Encouraging results were obtained following the administration of Epoetin alfa to anemic patients with solid cancers (Miller CB, Platanias LC, Mills SR, et al. *J Nat Cancer Inst* (1992) 84: 98-103), lymphoproliferative disorders such as malignant lymphoma and hematopoietic stem cell disorders (Cazzola M, Ponchio L, Beguin Y, et al. *Blood* (1992) 79: 29-37), and multiple myeloma (Barlogie B, Beck T. *Stem Cells* (1993) 11: 88-94, Beck JT, Hayden K, Hutchins L, et al. *Proc Am Soc Clin Oncol* (1992) 11: Abstract 1228. Ludwig H, Fritz E, Kotzmann H, Gisslinger H. *New Engl J Med* (1990) 322:1693-1699. Ludwig H, Fritz E, Leitgeb C, et al. *Ann Oncol* (1993) 4: 161-167).

Cancer is frequently associated with significant anemia, and has traditionally been treated by blood transfusion. Anemia may result from the disease itself, the effect of concomitantly administered chemotherapeutic agents, or a combination of both. The condition often takes on the characteristics of the anemia of chronic disease (ACD). ACD is associated with erythroid hypoplasia of the bone marrow, a somewhat shortened circulating life of red cells and decreased bone marrow re-utilization of iron. Clinical experience has been collected over the past years to show that Epoetin alfa can correct anemia in cancer patients at doses several times higher than those shown to be effective in renal patients. About 50-60% of anemic cancer patients receiving chemotherapy responded with a hemoglobin rise of at least 2 g/dL to Epoetin alfa therapy given three times weekly at a dose of 150 IU/kg over a period of 12 weeks (Abels RI, Larholt KM, Krantz KD, Bryant EC. *Proceedings of the Beijing Symposium.* Alpha Medical Press, Dayton, Ohio, 1991:pp 121-141). In a subsequent open-label dose titration study, doses up to 300 IU/kg, were sometimes required, demonstrating the relative resistance to the effect of erythropoietin in these patients. If erythropoietin levels are measured, they are

found to be within the normal range, but inappropriately low for the degree of anemia: there is a blunted erythropoietin response.

In a series of controlled clinical trials, anemic cancer patients receiving cyclic platinum or non-platinum containing chemotherapy were treated with placebo or Epoetin alfa (150 IU/kg t.i.w.). In these trials, Epoetin alfa was shown to increase hematocrit and decrease transfusion requirements after the first month of therapy ((Abels RI, Larholt KM, Krantz KD, Bryant EC. Proceedings of the Beijing Symposium. Alpha Medical Press, Dayton, Ohio, 1991:pp 121-141). In 1994, the Product Licence for Epoetin alfa was extended in several countries to include "the treatment of anemia in adult cancer patients receiving platinum containing chemotherapy regimens". However, more data needed to be collected to establish the efficacy of Epoetin alfa in cancer patients treated with non-platinum and platinum containing chemotherapy.

For patients receiving platinum-based chemotherapy, the Committee for Proprietary Medicinal Products (CPMP)-approved Summary of Product Characteristics specifies that epoetin alfa is indicated to treat anemic patients with an initial dose of 150 IU/kg s.c. t.i.w. (Subcutaneously, three times weekly) and a target hemoglobin level of approximately 12 g/dL. After four weeks of therapy, the dose may be adjusted up to 300 IU/kg t.i.w. based on hemoglobin and reticulocyte response. Hemoglobin status should be checked periodically, and iron status should be evaluated prior to and during treatment; iron supplementation should be administered if necessary. Therapy should continue until one month after the end of chemotherapy.

Despite apparent success in using erythropoietin in conjunction with an anti-tumor therapy in treating anemia, there is room for improvement in terms of effective dosing regimens, patient benefit, and cost-effective use of EPO. According to a recent review of clinical trials involving EPO response rates in patients receiving platinum containing chemotherapeutics, the percentage of patients who responded to EPO ranged from 36 – 82% for all trials considered, and from 50 - 79% for trials with similar response criteria. This wide variety of response rate was partly due to clinical trial design, but was also attributed to lack of a strong predictor of EPO response in this patient population (Fjornes, T. *J Oncol Pharm Practice* (1999). 5(1) 22 – 31). Clearly the blunted erythropoietin response in subjects with malignancy requires more study for effective dosing regimens.

The effect of Epoetin alfa on raising hemoglobin (Hb) levels in anaemic cancer patients has been demonstrated to lead to a concordant increase in quality of life (QoL) (Glasby et al, 1997, Demitri et al, 1998). To identify the Hb level at which QoL was optimised, a novel analytic approach, the incremental analysis, was applied to clinical and outcomes data from these two studies of 4,382 anaemic cancer patients receiving Epoetin alfa and chemotherapy. QoL was assessed using the linear analogue scale assessment (LASA) and the Functional Assessment of Cancer Therapy – anemia FACT-An) scale. The results, independently observed in both of these studies, demonstrated a statistically significant ($p<0.01$) nonlinear relationship between Hb level and QoL. Epoetin alfa-related increases in Hb were associated with QoL improvement in the Hb range 8-14g/dl. The largest improvement in QoL for each 1g/dl change in Hb occurred when Hb increased from 11 to 12g/dl (range 11 – 13). This relationship was maintained after controlling for tumour type and status, transfusions, number of days on study, the extent of chemotherapy or radiotherapy, and other factors such as nausea, pain etc. The conclusions – that improvements in Hb related to Epoetin alfa treatment were associated with improvement in QoL - suggest that the optimal management of Hb levels contributes significantly to improving QoL of anemic cancer patients receiving chemotherapy.

Decreasing the onset or severity of anemia is a desirable effect of EPO dosing regimens, resulting in increased Quality of life and reduced Fatigue. However the ultimate goal of any chemotherapeutic regimen is to prevent progression of the malignancy, reduce or eliminate the primary tumor, and preserve the life of the patient. It has been proposed that in addition to affecting the well being of the patient, that EPO may act by reducing hypoxia, particularly tumor hypoxia, which is higher than normal tissue. Most solid tumors exhibit physiological conditions different than normal tissue, including regions of hypoxia (low oxygen), low pH, and low glucose levels. This is thought to contribute to multi-drug resistance, including to the drugs etoposide, doxorubicin, camptothecin, and vincristine (Akihiro, T., Takashi, T. *Anti-Cancer Drug Des.* (1999). 14(2) 169-177). In a recent report, SCID (severe combined immunodeficient) mice containing human ovarian cancer xenografts were examined for response to cisplatin versus cisplatin+EPO. For animals engrafted with small tumors, a significant improvement in tumor regression was seen in the group of mice receiving cisplatin+EPO compared with cisplatin alone, thus supporting the implication of oxygen sensitization of the tumor (Silver, D.F., Piver, M.S. (1999).

Gynecol. Oncol. 73(2) 280–284). However this hypothesis has not been confirmed in human subjects, due to the complexity of the clinical trial conditions and the much higher costs associated with longer term trials. The literature is silent concerning the successful use of EPO to enhance tumor response to chemotherapeutic agents in humans, and there is no demonstration on patient survival when administered an EPO regimen in conjunction with a chemotherapeutic regimen.

International patent application WO9810650 describes a method of treating endothelial injury. The concurrent use of EPO with a chemotherapeutic agent is described, but does not teach enhanced tumor response or enhanced patient survival.

International patent application WO9952543 describes pharmaceutical compounds comprising erythropoietin for the treatment of cancer. The concurrent use of EPO with a chemotherapeutic agent is not described. This publication describes a small, uncontrolled study of five (5) patients who received recombinant human erythropoietin for 14 to 85 weeks beyond an initial 12-week course of EPO treatment. The initial EPO treatment was conducted to evaluate safety and tollerance of EPO in multiple myeloma patients and is described by Mittleman *et al.* in *Acta Haematol* (1997). 98 204 – 210. The authors then conducted a series of mouse model experiments, where mice bearing a "progressive myeloma" were treated with various dosing regimens of recombinant human EPO. This reference does not teach dosing regimens suitable for treatment of human malignancies using EPO. Further it is not predictable that the results seen in a mouse myeloma model would translate into other tumor types, or would indicate success in humans. For example in experiments conducted in SCID mice bearing human ovarian cancer, mice treated with EPO alone (a control group) showed no changes in tumor growth as a result of EPO administration. (Silver *et al* (1999)). These results described for the small, uncontrolled human experiments are not instructive in such that they lack sufficient control to allow for interpretation of the drug's (EPO) effects on the patient's health, specifically tumor response. This reference does not describe the use of EPO in a concurrent dosing regimen with another chemotherapeutic agent in order to enhance tumor response to the chemotherapeutic.

The present invention provides the surprising discovery that an EPO regimen in conjunction with a chemotherapeutic regimen provides greater tumor response and greater patient survival probability compared to a chemotherapeutic regimen alone. This unmet need of improved tumor response and survival could not be predicted from

prior clinical studies that examined the effects of using an EPO regimen to prevent, improve, or ameliorate anemia or to improve Quality of Life. The present invention describes a method to treat patients who suffer from cancer and are either currently receiving or are scheduled to receive non-platinum and platinum containing chemotherapeutics concurrently with an improved EPO dosing regimen. The present invention also provides a computer based metric system to tailor the dosage and schedule of the EPO treatment such that the patient receives optimum benefit in terms of increased hemoglobin and reticulocyte production.

SUMMARY OF THE INVENTION

The present invention provides a method to treat anemic and non-anemic subjects having malignancies who receive non-platinum and platinum antitumor agent containing chemotherapy such that the overall survival is increased.

The present invention provides algorithms for prediction of early response to erythropoietin therapy related to changes in ferritin, hemoglobin and transferrin receptor levels for subjects who receive non-platinum and platinum containing chemotherapy.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1: Time to First Transfusion or Hemoglobin Below 8 g/dL After Day 28 (Efficacy Population).

Figure 2: Mean Biweekly Hemoglobin Level (Efficacy Population).

Figure 3: Mean Biweekly Hematocrit Level (Efficacy Population).

Figure 4: Mean Biweekly Reticulocyte Count (%) Assessed Manually or Automatically (Efficacy Population).

Figure 5: Mean Biweekly Reticulocyte Count (%) Assessed Automatically (Efficacy Population).

Figure 6: Course of Hemoglobin (g/dL) by Hemoglobin Stratum (Efficacy Population).

Figure 7: Mean Weekly Dose of Study Drug (Intent-to-Treat Population).

Figure 8: Kaplan-Meier Estimates of Survival.

DETAILED DESCRIPTION OF THE INVENTION

The erythropoietin is present in the compositions in therapeutically effective amounts. "Erythropoietin" shall include those proteins that have the biological activity of human erythropoietin, as well as erythropoietin analogs, erythropoietin isoforms, erythropoietin mimetics, erythropoietin fragments, hybrid erythropoietin proteins, fusion proteins oligomers and multimers of the above, homologues of the above, glycosylation pattern variants of the above, and muteins of the above, regardless of the biological activity of same, and further regardless of the method of synthesis or manufacture thereof including but not limited to, recombinant whether produced from cDNA or genomic DNA, synthetic, transgenic, and gene activated methods. Specific examples of erythropoietin include, Epoetin alfa (EPREX®, ERYPO®), Novel erythropoiesis stimulating protein (NESP) (a hyperglycosylated analog of recombinant human erythropoietin (Epoetin) described in European patent application EP640619), human erythropoietin analog – human serum albumin fusion proteins described in the international patent application WO9966054, erythropoietin mutants described in the international patent application WO9938890, erythropoietin omega, which may be produced from an Apa I restriction fragment of the human erythropoietin gene described in United States patent 5,688,679, altered glycosylated human erythropoietin described in the international patent application WO9911781, PEG conjugated erythropoietin analogs described in WO9805363 or United States patent 5,643,575. Specific examples of cell lines modified for expression of endogenous human erythropoietin are described in international patent applications WO9905268 and WO9412650. The generally preferred form of EPO is purified, recombinant human EPO (rhEPO), distributed under the trademarks of EPREX® or ERYPO®. Epoetin alfa (EPREX®, ERYPO®) is a sterile, clear, colourless, aqueous solution for injection, that is provided in prefilled, single-use or multi-dose quantities.

EPO is administered by any suitable means, as would be apparent to one skilled in the art. The phrase "therapeutically effective" as used herein will be from about 1 to 500 I.U./kg body weight and more preferably from 50 to 300 I.U./kg body weight especially when erythropoietin is administered via subcutaneously. The preferred

methods of administration are intravenous (iv) and subcutaneous (sc), with subcutaneous being generally preferred. EPO is administered within the range of about 100 – 300 U/kg per dose, three to five times per week. A preferred initial dosing regimen is about 150 U/kg sc, three times per week. For patients who show a blunted response to the initial dose using predictive indicators, including those described herein, the preferred dosing regimen is about 300 U/kg sc, three times per week. EPO administration is delayed or withheld if the patient, male or female, exhibits a hemoglobin level in excess of about 15 g/dL.

The term "concurrent" as used herein, means that a pharmaceutically effective amount of a EPO dosing regimen and an anti-tumor agent dosing regimen are administered during the same period of time such that the patient receives the benefit of both agents alone and achieves a synergistic effect of the combination of the two agents. Synergy refers to a combined pharmacological effect that exceeds the anticipated result based on the amount of administration of either single agent.

It is readily apparent to those skilled in the art that a wide variety of non-platinum and platinum containing anti-tumor agents are suitable for use in the methods of the present invention. Platinum containing anti-tumor agents include, but are not limited to, cisplatin (cis-dichlorodiamineplatinum). Non-platinum containing anti-tumor agents include, but are not limited to, cyclophosphamide, fluorouracil, epirubicin, methotrexate, vincristine, doxorubicin, bleomycin, and etoposide. Each anti-tumor agent is administered within the therapeutically effective amounts, which are well known in the art, and vary based on the agent used, the type of malignancy, and other conditions.

It is also readily apparent to those skilled in the art that a wide variety of tumor types, or malignancies, are treatable according to the methods of the present invention. Such tumor types include, but are not limited to, solid tumors, hematological tumors, sarcomas, carcinomas, neoplasms, as well as tumors of the breast, Non-hodgkins lymphoma, myeloma, Hodgkin's lymphoma, leukemia, colon, rectal, colorectal, stomach, gastrointestinal, ovarian, lung, pancreas, and prostate.

Anemia is a condition marked by decreases in hemoglobin (Hb) levels defined herein as ≤15.0g/dL (9.30 mmol/l) for male subjects and ≤13.0g/dL (8.06mmol/l) for female subjects. Mildly anemic conditions are defined herein as Hb level ≤13.0 g/dL

(8.06mmol/l) for males and ≤12.0 g/dL (7.44mmol/l) for females. Severely anemic conditions are defined herein for both sexes as Hb ≤10.5 g/dL, with further medical intervention, typically in the form of blood transfusion, commonly administered at Hb <9g/dL, although transfusions are not common at hemoglobin levels above 9.0 g/dL. It is assumed that worsening anemia is a likely consequence of further chemotherapy and/or the underlying disease. Concurrent dosing regimens of EPO with an anti-tumor agent are conducted preferrably when a subject exhibits severe anemia, more preferably when a subject is mildly anemic, and still more preferably when the subject is at the low range of normal, about 15g/dL for a male subject and about 13g/dL for a female subject. Administration of EPO to a subject with > 10.5g/dL provides a preferable response in relation to amelioration, or reversal of anemia in subjects receiving concurrent administration of a chemotherapeutic agent and EPO. Early treatment with EPO can prevent worsening anemia requiring transfusion.

For ease of operation it is advised that epoetin treatment be started at the beginning of the next chemotherapy cycle. This allows accommodation of the study visit schedule without undue disturbance to the subject's planned clinic attendances. The traditional treatment for severe anemia is blood transfusion. These are administered according to clinical need, although transfusions are not common or preferred at hemoglobin levels above 9.0 g/dL. Although subject to extensive screening, blood allogenic blood transfusion is not without risk of acquired infections, primary concern is hepatitis (Dodd RY. N Engl J Med 192;327:419-421. Waymack JP *Infections in Surgery* (1990). July: 41-47. Busch MP, Lee T Heitman J. *Blood* (1992). 80(8): 2128-2135).

Quality of life is usually affected by malignancy, e.g., due to the underlying disease, effects of therapy and the psychological burden of coping with cancer. Fatigue is the most frequently reported symptom in cancer patients and impairs significantly their quality of life (Winningham ML, Nail LM, Barton Burke M, et al. *Oncol Nursing Forum* (1994) 21: 23-34) Anemia contributes to fatigue and to the reduction in quality of life. The effects on fatigue (FACT An) and quality of life (ECOG performance score, Cancer Linear Analogue Scale, SF36) of early intervention and/or treatment of anemia with Epoetin alfa can be alleviated with concurrent use of EPO during chemotherapy with non-platinum and platinum containing therapeutics. Concurrent administration of EPO with a chemotherapeutic agent provides improved physical performance and well being. The improved physical performance and improved well being is provided to subjects

who exhibit a partial response, and particularly a complete response to the chemotherapeutic agent / EPO concurrent dosing regimen.

Subjects treated with a chemotherapeutic agent / EPO concurrent dosing regimen are provided an enhanced probability of survival. The dosing methods and pharmaceutical formulations of the present invention are preferred for subjects with particular tumor types, including but not limited to, breast, myeloma, and ovarian tumors. Other tumor types that are suitable for the methods of the present invention are determined by monitoring patient survival over time to assess the overall mortality rate of patients receiving EPO versus placebo. At any time point the patient populations, either EPO treated or placebo, are counted to determine the number of living patients at the time point. Patients who are unavailable for follow – up analysis are conservatively scored as dead for purposes of scoring the patient.

Predictors of response can be a valuable clinical tool for use in the selection of optimal treatment modes. Various response predictors to treatment with exogenous EPO have been proposed. Some groups have reported that pre-treatment EPO levels themselves are indicative of response (Marsden JT, Sherwood RA, Hillis A, Peters TJ. *Ann Clin Biochem* (1992) 30: 205-206. Fischl M, Galpin JE, Levine JD, et al. *N Engl J Med* (1990) 322: 1488). In recent work published by Ludwig et al. (Ludwig H, Fritz E, Leitgeb C, et al. *Blood* (1994) 84 (4): 1056-1063), an algorithm with high predictive power was developed based on serum EPO level and hemoglobin increase after two weeks of Epoetin alfa therapy. Alternatively, serum ferritin levels after two weeks of treatment with Epoetin alfa were reported to strongly indicate responsiveness. These algorithms were assessed and compared with the earlier findings of predicting response by examining early changes (after two and four weeks) in hemoglobin level, and reticulocyte count (Henry D, Abels R, Larholt K. *Blood* (1995) 85 (6): 1676-1678) to establish whether EPO levels and hemoglobin change and/or serum ferritin levels measured two weeks after and/or hemoglobin and reticulocyte change measured two and four weeks after the start of treatment with Epoetin alfa indicate eventual responsiveness to erythropoietin therapy. An algorithm for prediction of early response to erythropoietin therapy related to changes in ferritin, hemoglobin and transferrin receptor levels for subjects who receive non-platinum and platinum containing chemotherapy allows the method of treatment, including dose concentration and regiment, to be altered such that the patient receives the optimum benefit of the EPO treatment. This

algorithm yields cost effective use of EPO, and would be expected to reduce the overall Healthcare cost for EPO therapy.

The following examples illustrate the present invention without, however, limiting the same thereto.

EXAMPLE 1 - DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO ASSESS THE EFFECT OF EARLY INTERVENTION AND/OR TREATMENT WITH EPOETIN ALFA ON ANEMIA IN CANCER PATIENTS RECEIVING NON-PLATINUM AND PLATINUM CONTAINING CHEMOTHERAPY.

Overview of Study Design

This was a multicenter, randomized, double-blind, placebo-controlled study conducted in fifteen countries (Belgium, Czech Republic, France, Germany, Greece, Hungary, Ireland, Italy, Luxembourg, The Netherlands, Poland, Portugal, South Africa, Switzerland, and UK). To enroll subjects thought to be at high risk for the development of transfusion-dependent anemia, enrollment was restricted to subjects who had either a low baseline hemoglobin level (≤10.5 g/dL) at any time during chemotherapy or to those subjects whose hemoglobin had fallen substantially (≥1.5 g/dL per cycle or per month) since the beginning of the current course of chemotherapy such that it dropped to ≤12 g/dL. Subjects were predicted to receive chemotherapy for at least 12 to 24 weeks (or three to six chemotherapy cycles).

Three hundred seventy-five subjects (360 planned) with non-myeloid malignancies receiving non-platinum-containing chemotherapy were enrolled into the study. Subjects were stratified by tumor type (solid or hematological) and hemoglobin level (≤10.5 g/dL and >10.5 g/dL). Allocation to the hemoglobin strata (≤10.5 g/dL and >10.5 g/dL) was based on hemoglobin at the time of screening. Subjects were randomly assigned in a 2:1 ratio to receive 150 IU/kg epoetin alfa or placebo t.i.w. for either 1) the first four weeks if the subject was on continuous chemotherapy, 2) for the first on-study chemotherapy cycle if there were ≥21 days between the start of study medication and the end of the first on-study cycle, or 3) for the first two on-study cycles if there were <21 days between the start of study medication and

the end of the first on-study cycle. If, at the end of the initial dosing period the reticulocyte count increased ≥40,000/μL above baseline or the hemoglobin level rose ≥1 g/dL, study medication was to be continued at the same dose. If, at the end of the initial dosing period the reticulocyte count increased by <40,000/μL above baseline and the hemoglobin level rose <1 g/dL above baseline, the weekly dose of study medication was doubled to 300 IU/kg t.i.w.

Study drug was blinded for identity (epoetin alfa or placebo) but not for dose level (150 or 300 IU/kg after the initial four weeks), and was administered subcutaneously (s.c.). The protocol recommended that blood transfusions be performed as necessary during the study, but every effort should be made not to transfuse subjects with a hemoglobin level above 8 g/dL. If, at any time during the study, the hemoglobin level exceeded 15 g/dL, study drug was to be withheld until the hemoglobin level fell below 12 g/dL, and was to be restarted at a dose level approximately 25% below the dose level that was previously being administered. If the hemoglobin level was rising at a rate ≥2 g/dL per month or ≥2 g/dL per cycle, the dose of study drug was to be reduced by approximately 25% to maintain the rate of rise of hemoglobin to <2 g/dL per month (<2 g/dL per cycle).

Primary efficacy evaluations were based on transfusion requirements. Changes in hemoglobin levels, hematocrit levels, reticulocyte counts, testing predictive algorithms for response, and quality-of-life parameters were secondary evaluations.

Safety evaluations included assessments of the incidence and severity of adverse events, clinical laboratory tests, vital sign measurements, and physical examinations.

Study Population

OVERVIEW

Three hundred sixty subjects with non-myeloid malignancies receiving non-platinum-containing chemotherapy were to be enrolled in the study (375 actual). Subjects were enrolled according to the inclusion and exclusion criteria summarized below.

INCLUSION CRITERIA

Subjects enrolled in the study were required to meet the following inclusion criteria:

- Subjects had a confirmed diagnosis of non-myeloid malignancy for which non-platinum-containing chemotherapy was underway or imminent (noncyclic or cyclic with a minimum cycle duration of three weeks).
- Subjects had not been previously treated by platinum-containing chemotherapy for ≥3 months.
- Subjects were predicted to receive further chemotherapy for at least 12 to 24 weeks or three to six chemotherapy cycles.
- Subjects were to have an Eastern Cooperative Oncology Group (ECOG) performance score of 0, 1, 2, or 3
- Subjects were to have a life expectancy of six months or longer, based on the investigator's clinical judgment.
- Subjects, male or female, were to be at least 18 years old.
- Female subjects were to be postmenopausal for at least one year or surgically sterile, or using a reliable method of birth control and have a negative serum pregnancy test prior to study entry.
- Subjects were to have at any time of chemotherapy: a hemoglobin level ≤10.5 g/dL or, if greater than this value, a fall in hemoglobin level

≥1.5 g/dL per cycle or per month since the beginning of the current course of chemotherapy such that it has dropped to ≤12.0 g/dL.

- Subjects were to have laboratory values within the following limits after recovery from the previous chemotherapy cycle:
  - platelets >75,000 cells/μL
  - reticulocytes <125,000/μL
  - neutrophils >1,000/μL
- Subjects were to have read and signed the informed consent form after the nature of the study had been fully explained and the confidential follow-up form had been completed.

EXCLUSION CRITERIA

Subjects were not to be enrolled into the study if it were determined upon prestudy examination that they:

- had acute leukemias (acute lymphocytic leukemia, acute myelolytic leukemia) and other malignancies derived from the myeloid cell line;
- had myeloablative chemotherapy (with or without bone marrow or peripheral blood stem cell transplantation);
- had clinically significant disease/dysfunction of the pulmonary, cardiovascular, endocrine, neurological, gastrointestinal, or genitourinary systems not attributable to underlying malignancy or chemotherapy (adequately controlled diabetes mellitus was to be acceptable);
- had uncontrolled hypertension (i.e., diastolic blood pressure greater than 100 mm Hg) or a history of seizures;
- had evidence of untreated folate or Vitamin B_{12} deficiency;
- had received androgen therapy within two months of study entry;
- had an ECOG performance score of 4;

- had an acute major illness within seven days of study entry, or major infection within one month of study entry;
- received radiotherapy within 14 days prior to study entry;
- had surgery within seven days prior to study entry;
- had major bleeding within one month prior to study entry;
- received an allogeneic transfusion within two weeks prior to study entry;
- had a known hypersensitivity to epoetin alfa or one of its components;
- had been administered an experimental drug (not approved in the investigator's country) or used an experimental device within 30 days prior to study entry.

Study Drug Information

Epoetin alfa (EPREX or ERYPO) was formulated as a sterile, buffered solution containing 2.5 mg/mL human serum albumin and was supplied in pre-filled, single-use syringes containing 10,000 IU epoetin alfa in 1 mL phosphate buffer and 4,000 IU epoetin alfa in 0.4 mL phosphate buffer. The placebo was identical to the epoetin alfa solution, except that it did not contain the active ingredient.

The batch numbers for epoetin alfa were: 5M608T, 6D617T, 6E606T, 6J619T, 6M603T for the 10,000 IU/mL syringes; and 5L630T, 6E609T, 6G625T, 6J617T, 6M616T, 7E621T for the 4,000 IU/mL syringes.

The batch numbers for placebo were: 901511, 909607, 901704 for the 10,000 IU/mL syringes; and 902511, 910607, 902610 for the 4,000 IU/mL syringes.

For each subject, investigational sites were initially supplied with 120 syringes (42x4,000 IU/mL and 78x10,000 IU/mL) epoetin alfa or placebo. A second set of 120 syringes per randomized subject was supplied on the investigator's request (if required), according to subject weight, dose level,

and study duration. Subjects were generally only provided with a 2- to 4-week supply at any one time.

A label was affixed to each primary drug container with the following information:

- study/protocol number
- subjects number
- declaration (generic, strength)
- volume and galenic form
- expiratory date
- route of administration (s.c.)
- storage conditions
- sponsor identification
- instruction "for single use only"
- caution on limitation to investigational use only

A label was affixed to each secondary drug container with the following information:

- study/protocol number
- subjects number
- declaration (generic, strength)
- volume and galenic form
- expiratory date
- route of administration (s.c.)
- storage conditions
- sponsor identification
- instruction "for single use only"
- caution on limitation to investigational use only
- space for investigator name
- safety instructions (e.g., "keep out of reach of children")

In addition, sealed envelopes containing the study drug identification, formulation code, and manufacturer's lot numbers were provided to the investigator.

Randomization and Blinding

Study drug was blinded for identity (epoetin alfa or placebo) but not for dose level (150 or 300 IU/kg). Each subject was randomly assigned in a double-blind manner to receive 150 IU/kg epoetin alfa or placebo in a 2:1 ratio balanced by using permuted blocks, according to a randomization schedule prepared by RWJPRI. A prospective stratification into tumor type (solid vs. hematological) and hemoglobin level (>10.5 g/dL or ≤10.5 g/dL, based on hemoglobin at the time of screening) was applied in order to achieve comparable treatment groups with respect to these variables

One subject (placebo group) completed the screening assessments but decided to withdraw from the study before taking any study drug. Since no study drug was taken and no study assessments were performed on this subject, the treatment number was re-assigned to a new subject (1092, placebo group).

Dosage and Administration

Study medication (150 IU/kg epoetin alfa or placebo) was administered by s.c. injection, t.i.w., with each dose separated by at least two days. If, at the end of the initial dosing period the reticulocyte count had increased by <40,000/μL above baseline and the hemoglobin level had risen <1 g/dL above baseline, the weekly dose of study medication was doubled to 300 IU/kg t.i.w. Otherwise, the 150 IU/kg dose was maintained. Treatment was to continue for 12 to 24 weeks (or three to six chemotherapy cycles) plus four weeks post-chemotherapy.

If a subject's hemoglobin exceeded 15 g/dL at any time during the study, study medication was withheld until the hemoglobin decreased below 12 g/dL, and then was restarted at a dose approximately 25% below that which was being administered. If the hemoglobin level rose at a rate ≥2 g/dL per month or ≥2 g/dL per cycle, the dose of study drug was to be reduced by

approximately 25% to maintain the rate of rise of hemoglobin to <2 g/dL per month (<2 g/dL per cycle).

Tr atment Compliance

Subjects were instructed to return all used and unused medication containers to the investigator. The investigators were instructed to keep a detailed inventory of all study medication received, dispensed, and returned.

Concomitant Therapy

The concomitant use of androgens was prohibited during the study; the use of licensed white cell growth factors was not prohibited. Iron supplementation was recommended to be given to maintain appropriate iron availability and iron stores. For all subjects, an oral daily dose of 200 mg elemental iron was recommended. If during the study the transferrin saturation was not maintained above 20% with oral iron, i.v. iron, preferably iron saccharate was recommended; the use of iron dextran was not allowed. All iron supplementation administered was to be recorded in the CRF. All concomitant medications administered during the study were to be recorded on the CRF, including drugs, dosages, and schedule of administration.

Study Evaluations

TIME AND EVENTS SCHEDULE

Table 1 provides an overview of the key study procedures that were conducted.

Prestudy screening. Subjects were screened within seven days prior to study entry. Screening procedures included complete medical histories; previous chemotherapy (number of cycles, drugs, and dosage) for the past three months; hemoglobin level at the beginning of the current cycle of chemotherapy; physical examinations including vital sign measurements and clinical signs and symptoms of malignant disease; history and staging of malignant disease; concurrent therapy; transfusion information for the previous three months including hemoglobin level prior to transfusion, volume, and type of product transfused; determinations of serum iron, serum ferritin, and transferrin; serum erythropoietin level; soluble transferrin

receptors (selected centers); C-reactive protein (selected centers); fibrinogen (selected centers); determination of the ECOG performance score; completion of the quality-of-life questionnaires: Functional Assessment in Cancer Therapy-Anemia Scale (FACT-An), Cancer Linear Analog Scale (CLAS), and Medical Outcomes Study-Short Form-36 (SF-36) completion of the subject burden questionnaires on employment status and transfusions; completion of a work loss diary card.

Clinical laboratory tests performed at screening included (after subjects' recovery from previous chemotherapy treatment):

Hematology:

- hemoglobin
- hematocrit
- total erythrocyte (RBC) count
- total leukocyte (WBC) count with differential
- platelet count
- reticulocyte count (μL^{-1})

Serum Chemistry:

- calcium
- sodium
- potassium
- chloride
- glucose
- phosphorus
- bicarbonate
- creatinine
- uric acid
- BUN
- LDH
- alkaline phosphatase
- total protein
- cholesterol

- triglycerides
- total bilirubin
- serum glutamic-oxaloacetic transaminase (SGOT; AST)
- serum glutamate pyruvate transferase (SGPT; ALT)
- gamma-GT
- C-reactive protein (optional)
- fibrinogen (optional)

Urinalysis:

- pH
- glucose, ketones, blood, nitrite, and protein
- leukocytes

Table 1: Schedule of Key Study Procedures

Procedure	Prestudy[a]	Treatment Phase: Chemotherapy (Weeks 1-24)	Post-Chemotherapy (Weeks 25-27)	Study Completion/ Termination[b]
Medical history	X			
Physical examination	X			X
Vital signs	X[f]	X[f]	X[f]	X
Malignancy staging	X			X
Hematology	X	X[c,d]	X	X
Serum chemistry	X			X
Urinalysis	X			X
Iron parameters	X	X[c,e]		X
Erythropoietin levels	X	X[c]		
Transferrin receptors (selected centers)	X	X[c]		
Study drug administration		X	X	
Response to chemotherapy				X
Transfusion data	X	X		X
ECOG performance score	X	X[g]		X
Quality-of-life questionnaire	X	X[g]		X
Subject burden questionnaires	X	X[h]		X
Subject burden diary card	X	X	X	X
Adverse event collection		X	X	X

[a] All procedures performed within seven days of first study drug administration.
[b] All procedures performed within five days after last study drug administration.
[c] Must be exactly two weeks after start of study drug administration.
[d] Performed every two weeks (or after each half-way interval of chemotherapy cycle).
[e] Performed after four weeks (or at the end of the first on-study chemotherapy cycle) then every four weeks (or after each chemotherapy interval).
[f] Prior to all procedures or prior to dosing with study drug and performed every two weeks.
[g] Completed on Week 4 and Week 16 (or before the second and fifth on-study chemotherapy cycle).
[h] Completed every four weeks.

Treatment phase: Chemotherapy (Weeks 1-24). Study medication was administered as described in Dosage and Administration. Hematology,

including hemoglobin, hematocrit, erythrocyte count, leukocyte count with differential, platelet count, and reticulocyte count was performed every two weeks (or after each halfway interval of a chemotherapy cycle). During the first chemotherapy cycle, all blood sampling was performed after two weeks on study treatment. Sample collection for iron parameters was performed after exactly two weeks on study treatment, then after four weeks (or at the end of the first on-study chemotherapy cycle), then every four weeks (or after each chemotherapy interval). Determination of serum erythropoietin levels and soluble transferrin receptors was performed at the end of the second week on study treatment (immediately before the first scheduled study drug administration of the third week). Vital sign measurements were performed every two weeks. The ECOG performance score, as determined by the investigator, was to be completed on Week 4 or before the start of the second on-therapy chemotherapy cycle and Week 16 or before the start of the fifth on-study chemotherapy cycle; the quality-of-life questionnaires (FACT-An, CLAS, and SF-36) were also to be completed at this time. The subject burden questionnaire was to be completed for transfusions and unscheduled physician visits after each chemotherapy cycle or every four weeks, and for study drug administration after the first chemotherapy cycle or the first four weeks on study treatment only. Subjects were to keep a work loss diary. A description of any concurrent chemotherapy and any concurrent therapy other than chemotherapy during the study was also to be recorded, including drugs, dosages, and schedule of administration. Subjects were encouraged to report adverse events throughout the study.

Treatment Phase: Post-Chemotherapy (Weeks 25-27). Study medication was administered as described in Dosage and Administration. Hematology, including hemoglobin, hematocrit, erythrocyte count, leukocyte count with differential, platelet count, and reticulocyte count as well as vital sign measurements, were performed during the second week of post-chemotherapy. Subjects were to continue to keep a work loss diary. Reporting of adverse events was to continue during the postchemotherapy period.

Study completion/termination. A study termination visit was scheduled within five days of completing the study (i.e., four weeks after the end of chemotherapy) or upon early withdrawal from the study. At study completion or termination, the following procedures were repeated: physical examination including vital sign measurements and clinical signs and symptoms of malignant disease; malignancy staging; hematology including hemoglobin, erythrocytes, leukocyte count with differential, platelet count, and reticulocyte count; serum chemistry; serum iron, transferrin, and serum ferritin; transfusion information including hemoglobin level prior to transfusion, volume, and type of product transfused; details of chemotherapy and concurrent therapy; and assessment of the subjects' response to chemotherapy. In addition, the quality-of-life and subject burden questionnaires were to be completed, the last work loss diary was to be collected, and the ECOG performance score, as determined by the investigator, was to be performed.

Post-study follow up. Survival data (i.e., survival/death, date of death, whether or not death was caused by disease progression) were to be collected for the post-study period ending three months after the last subject completed the study and also for the post-study period ending 12 months after the last subject completed the study. Results will be reported separately.

EFFICACY EVALUATIONS

Efficacy evaluations were based on comparisons between treatment groups of the effectiveness of early intervention or treatment with epoetin alfa on anemia in cancer subjects undergoing non-platinum-containing chemotherapy. Primary efficacy evaluations were based on transfusion requirements. Changes in hemoglobin levels, hematocrit levels, reticulocyte counts, testing predictive algorithms for response, quality-of-life parameters and subject burden and work loss were secondary evaluations.

SAFETY EVALUATIONS

Safety evaluations included assessments of the incidence and severity of adverse events, clinical laboratory tests, vital sign measurements, and physical examinations.

Adverse Events

A treatment-emergent adverse event was defined as any noxious or unintended event that was new in onset or aggravated in severity or frequency following entry into the study, whether or not associated with the use of study drug. Any pathological finding on physical examination or diagnostic procedure that was new in occurrence or exacerbated in comparison with the subject's status at study entry was considered to be a treatment-emergent adverse event if it required any medical intervention. Subjects were encouraged to report adverse events throughout the course of the trial or in response to general nondirected questioning. Adverse events were also identified by the investigator by comparing the medical histories, prestudy physical examinations, and prestudy laboratory test results to those conducted during the study evaluation period.

All treatment-emergent adverse events were recorded by the investigator on the subject's CRF regardless of seriousness, severity, or presumed relationship to study drug as assessed by the investigator. Whenever possible, diagnoses were given when signs and symptoms were due to a common etiology. Other information recorded on the CRF included the date and onset of the event, duration, control measures taken (e.g., temporary or permanent discontinuation or reduction of study drug, or other treatment), the outcome (resolved, persisted, or unknown), and the date of resolution of the event.

Serious adverse events were defined as those events that presented a significant threat to the well-being of the subject. Serious adverse events included any event that was fatal, life-threatening, permanently or significantly disabling, required hospitalization or prolonged hospitalization, resulted in long-term outpatient treatment, or was a congenital anomaly, cancer, or overdose. Investigators were instructed to report all serious adverse events immediately.

Clinical Laboratory Tests

Standard clinical laboratory tests, including hematology and reticulocyte count, serum chemistry, and urinalysis were performed during screening and

were repeated at study completion or termination. Hematology and reticulocyte count were repeated every two weeks (or after each halfway interval of a chemotherapy cycle) and at study completion or subject withdrawal.

Vital Signs and Physical Examinations

Vital sign measurements and physical examinations were performed during screening and vital sign measurements were repeated every two weeks. Vital sign measurements and physical examinations were repeated at study completion or subject withdrawal.

Data Quality Assurance

Before study initiation, the protocol and statement of informed consent were approved by independent Ethics Committees. Steps taken to ensure accurate and reliable data included prescreening investigators and study centers, review of protocol procedures with the principal investigator and associate personnel, and on-site monitoring of study records. Instructions for completion of CRFs, quality-of-life questionnaires, and subject diaries were also provided and reviewed prior to the start of the study. Data obtained throughout the study were entered on the subjects' CRFs and were reviewed on an ongoing basis. The investigator signed and dated the Investigator's Statement on the final form. In addition, the study was audited by a clinical quality assurance department.

Removal of Subjects from Therapy or Assessment

Reasons for subject withdrawal from the study before completion that were specified in the protocol included the development of a severe or alarming adverse event, development of a significant intercurrent illness, subject request, subject lost to follow-up, and investigator request. When a subject discontinued from the study, the reason was recorded on the CRF with the subject's discontinuation/completion information, and a physical examination; vital sign measurements; and clinical laboratory tests including hematology, blood chemistry, and urinalysis were repeated. Dropouts were not replaced.

Statistical Methods

EFFICACY

Analys s Plann d

The sample size calculation was based on the ability to detect an odds ratio of 2 between success and treatment, where success is defined as the absence of any transfusion after the end of the first four weeks of treatment. The following assumptions on success rates per stratum and treatment arm (placebo:epoetin alfa) were to be made:

- Solid tumors - hemoglobin level ≤10.5 g/dL: 0.50/0.67
- Solid tumors - hemoglobin level >10.5 g/dL: 0.55/0.71
- Hematologic tumors - hemoglobin level ≤10.5 g/dL: 0.45/0.62
- Hematologic tumors - hemoglobin level >10.5 g/dL: 0.50/0.67

Based on the Cochran-Mantel-Haenszel test, the sample size needed to detect these differences with a power of 90% at the 0.05 significance level (one-sided) and a treatment assignment of 2:1 was determined to be 360 subjects, 120 in the placebo-treated group and 240 in the epoetin alfa-treated group.

For the analysis all statistical tests were to be two-sided. The main effects were to be tested using an alpha level of 0.05 and interactions tests were to be conducted using an alpha level of 0.10.

Study populations. The intent-to-treat population included all subjects randomly assigned to a treatment group. The efficacy population included all subjects randomly assigned to a treatment group who were in the study for more than one month (>28 days). The safety population included all subjects randomly assigned to a treatment group who received at least one dose of study drug and for whom safety information was available.

Primary efficacy variable. The proportion of subjects not transfused (successes) after the first four weeks of treatment was to be analyzed for the intent-to-treat and for the efficacy populations, where the intent-to-treat analysis was to be the main focus of the analysis. Subjects who were on study for less than or equal to one month (≤28 days) were to be counted as

transfused for the intent-to-treat analysis. Transfusions occurring during Month 1 were not included because observed treatment effects would not be expected until after this period. The analysis was to be carried out using a logistic regression model including terms for the main effects of treatment group, primary tumor type (solid vs. hematologic), hemoglobin stratum (≤10.5 g/dL or >10.5 g/dL), and interaction terms for treatment by tumor type and treatment by hemoglobin stratum. Interaction terms with a p-value >0.1 were to be dropped. From the resulting model the p-value for Wald's chi-square was to be used for the treatment effect.

Secondary efficacy variables. Secondary variables except final response were to be analyzed for the efficacy population. Final response was to be evaluated for those subjects who completed eight weeks of treatment. Secondary variables included change of hemoglobin level, hematocrit level, and reticulocyte count from baseline to last value; the proportion of subjects transfused or with a hemoglobin level below 8 g/dL; cumulative transfusion rate relative to the observation period excluding the first month; time to first transfusion or hemoglobin level <8 g/dL after the first month; change in the performance status from baseline to the last value on study; and quality-of-life assessments.

Three aspects of response were to be analyzed, including responders (subjects with an increase in hemoglobin level ≥2 g/dL), correctors (subjects reaching a hemoglobin level of 12 g/dL), and final response. Final response, defined as the change in hemoglobin level from baseline to the end of the study, was to be tabulated for all subjects who had completed at least eight weeks of treatment. Outcome categories were to include: rising response (≥2 g/dL), holding response (0-2 g/dL), decline (any fall in hemoglobin level not requiring transfusion), or non-responding (transfusion required). Since hemoglobin levels are not reliable after blood transfusions, they were not to be taken into account for response calculation during four weeks after a blood transfusion.

The following three algorithms for predicting final response outcomes to epoetin alfa in cancer subjects were to be evaluated in this trial: change in

erythropoietin level and hemoglobin level from baseline to two weeks on study medication, serum ferritin value after two weeks on study medication, and change in hemoglobin level and reticulocyte count from baseline to two and four weeks (or before the start of next chemotherapy cycle) on study medication. The correlation between these algorithms and final response outcomes were to be examined and compared. The intensity of chemotherapy was also to be taken into account.

The primary quality-of-life analysis was to be performed for seven measures: the FACT-G and FACT fatigue subscales of the FACT-An questionnaire, all three CLAS scores, and the physical and mental summary scores of the SF-36 quality-of-life questionnaire. Quality-of-life change scores (follow-up minus baseline) were to be computed for each of the seven quality-of-life measures for each study subject for Week 4, Week 16, and study completion. A negative change score indicates a worsening quality of life, while a positive change score indicates an improved quality of life. All scoring of the quality-of-life measures were to be done according to developer specifications.

The quality-of-life intent-to-treat population was to be defined as those subjects who were randomized, received drug, and had a quality-of-life assessment completed at baseline and for at least one follow-up assessment. Change in the quality-of-life measures within and between treatment groups was to be assessed for the quality-of-life intent-to-treat population. Subgroup analyses were to be performed for 1) those subjects with hemoglobin stratum >10.5 g/dL versus those with hemoglobin stratum ≤10.5 g/dL; and 2) those subjects with solid versus hematologic tumors. Analysis of covariance was also to be conducted where the effect of epoetin alfa on quality of life was to be adjusted for significant confounding influences by selected clinical and demographic covariates. The covariates to be investigated as possible sources of confounding effects were to include: baseline hemoglobin level, tumor type, tumor response, demographics, and investigator site (investigator sites may be grouped to facilitate analysis). Correlational analysis was to be performed between change in hemoglobin and change in quality of life.

All statistical tests for quality-of-life were to be evaluated for significance using an alpha level of 0.05. Results were also to be reported after adjusting for multiple comparisons using a sequentially-rejective Bonferroni technique. All t-tests were to be two-tailed.

Post-study follow up survival data was to be reviewed and the results summarized for epoetin alfa and placebo groups was to be reported separately to the main study report.

Analyses Performed

Analyses were performed as planned, with the following minor exceptions:

- Two subjects whose blind was broken before the database was locked were excluded from the efficacy population.
- Since there was a slight difference between the treatment groups in baseline transfusion dependence, an additional logistic regression analysis was performed to correct for baseline transfusion dependence in addition to tumor type and hemoglobin stratum.
- Automatically assessed reticulocyte counts were analyzed separately. Because of the skewed distribution of the changes from baseline, a non-parametric test was considered more appropriate.
- Change in hemoglobin by tumor type (solid versus hematologic and by diagnosis of malignancy) was also analyzed.
- In addition to actuarial estimates of the probability to be transfused (or with Hb <8 g/dL), the monthly proportion of subjects transfused (or with Hb <8 g/dL) was tabulated.
- Cumulative transfusion rates were calculated for the transfused subjects only.
- Final response was also tabulated by potential predictors used in the predictive models.

- Retrospective classification of "gynecologic" and "other tumor types was performed.
- Retrospective classification of "other" reasons for withdrawal was performed.
- A retrospective assessment of the analysis method for reticulocytes was performed.

SAFETY

Analyses Planned

As stated in the protocol, safety was to be assessed by monitoring the incidence and severity of adverse events, and changes in the results of clinical laboratory tests, staging, vital sign measurements, and physical examinations.

All safety analyses were to be based on the safety population. The adverse event terms recorded on the CRFs were standardized for data summary purposes using the WHOART dictionary of terms. Adverse events were to be summarized by body system, preferred term, and included term for each treatment group. The severity of adverse events and relationship to study drug were to be summarized. A preferred term is the preferred medical terminology or categorization used to describe related included terms. An included term approximates the investigator's description of an adverse event. A summary of serious adverse events was to be provided. Separate summaries and listings of adverse events and of study completion information were to be provided for subjects who died or discontinued due to an adverse event.

Clinical laboratory tests and their changes from baseline were to be summarized for each timepoint of assessment, and changes from baseline to last value were to be summarized. Generic normal ranges were to be defined and all laboratory test values falling outside the generic normal range were to be flagged as high or low in the data listings.

Vital signs including temperature, pulse rate, blood pressure, and body weight were to be summarized. Changes in physical examination findings were to be listed and summarized by body system.

Changes in malignancy staging during the study were to be summarized and listed. Response to chemotherapy was to be summarized for discussion of chemotherapy intensity, treatment effect, and quality of life.

Analyses Performed

Analyses were performed as planned, with the following minor exceptions:

- Change of tumor staging was not evaluated because the staging was not performed uniformly.
- The analysis of changes of laboratory data from baseline has been restricted to changes from baseline to the last value on study, i.e., changes from baseline have not been summarized for each time point of assessment.

RESULTS

Demographic and Baseline Characteristics

Three hundred seventy-five subjects were enrolled at 73 sites in 15 countries, as indicated in Table 2. Approximately half of the subjects were enrolled in Germany (21%), the Netherlands (16%), and Great Britain (10%). By double-blind randomization in a 2:1 ratio, 251 subjects were assigned to receive epoetin alfa and 124 subjects were assigned to receive placebo. These 375 subjects were included in the intent-to-treat population.

Table 2: Subject Enrollment by Country (Intent-to-Treat Population)

Country	Epoetin Alfa (N=251)	Placebo (N=124)	Overall (N=375)
Germany	51 (20%)	26 (21%)	77 (21%)
Netherlands	42 (17%)	18 (15%)	60 (16%)
Great Britain	26 (10%)	13 (11%)	39 (10%)
Belgium	21 (8%)	12 (10%)	33 (9%)
Italy	20 (8%)	10 (8%)	30 (8%)
South Africa	17 (7%)	8 (7%)	25 (7%)
France	13 (5%)	8 (7%)	21 (6%)
Greece	12 (5%)	5 (4%)	17 (5%)
Switzerland	11 (4%)	5 (4%)	16 (4%)
Poland	10 (4%)	5 (4%)	15 (4%)
Portugal	10 (4%)	4 (3%)	14 (4%)
Hungary	8 (3%)	5 (4%)	13 (4%)
Czech Republic	6 (2%)	3 (2%)	9 (2%)
Ireland	2 (1%)	1 (1%)	3 (1%)
Luxembourg	2 (1%)	1 (1%)	3 (1%)

In the intent-to-treat population, demographic characteristics were generally comparable between the epoetin alfa and placebo treatment groups (Table 3). For all subjects, mean age was 58.7 years, mean weight was 67.6 kg, and mean height was 166 cm. There were twice as many women (67%) enrolled as men (33%) and the majority (96%) of subjects were of white racial origin.

In this study, a prospective stratification into tumor types (hematological or solid) and hemoglobin level (≤10.5 g/dL or >10.5 g/dL, based on hemoglobin at time of screening) was applied in order to maintain the 2:1 ratio of epoetin alfa subjects to placebo subjects in these strata. Overall, solid tumors were present in 54% of the subjects and hematological tumors (included non-Hodgkin's and Hodgkin's lymphoma) in 46% of subjects. Eighty-five percent of all the subjects were stratified to a hemoglobin ≤10.5 g/dL and 15% were stratified to a hemoglobin >10.5 g/dL.

Table 3: Demographic and Baseline Characteristics (Intent-to-Treat Population)

Characteristic	Epoetin Alfa (N=251)	Placebo (N=124)	Overall (N=375)
Sex			
Female	166 (66%)	85 (69%)	251 (67%)
Male	85 (34%)	39 (32%)	124 (33%)
Age (years)			
Mean±SD	58.3±14.18	59.5±13.91	58.7±14.09
Median	60.6	61.2	61.0
Range	18.7-84.9	21.1-88.6	18.7-88.6
Height (cm)	(N=251)	(N=122)	(N=373)
Mean±SD	166±9.0	166±10.0	166±9.3
Median	165	165	165
Range	144-196	148-196	144-196
Weight (kg)			
Mean±SD	67.4±13.19	67.9±12.99	67.6±13.11
Median	66.0	68.0	67.0
Range	41.0-119.0	44.0-110.7	41.0-119.0
Race			
White	242 (96%)	119 (96%)	361 (96%)
Asian	1 (<1%)	3 (2%)	4 (1%)
Black	4 (2%)	0 (0%)	4 (1%)
Other	4 (2%)	2 (2%)	6 (2%)
Tumor type[a]			
Solid	136 (54%)	66 (53%)	202 (54%)
Hematological[b]	115 (46%)	58 (47%)	173 (46%)
Hemoglobin stratum[a]			
≤10.5 g/Dl	209 (83%)	109 (88%)	318 (85%)
>10.5 g/dL	42 (17%)	15 (12%)	57 (15%)
Months since diagnosis[c]			
Mean±SD	35.3±47.39	31.1±40.34	33.9±45.17
Median	15.9	18.3	17.3
Range	0.2-323.7	0.5-248.3	0.2-323.7
Bone Marrow Involvement			
Primary			
Yes	65 (26%)	39 (32%)	104 (28%)
No	168 (67%)	78 (63%)	246 (66%)
Unknown	18 (7%)	7 (6%)	25 (7%)
Metastatic			
Yes	33 (13%)	22 (18%)	55 (15%)
No	176 (70%)	82 (66%)	258 (69%)
Unknown	42 (17%)	20 (16%)	62 (17%)
Chemotherapy within 3 months prestudy			
Yes	231 (92%)	114 (92%)	345 (92%)
No	20 (8%)	10 (8%)	30 (8%)
ECOG Performance score (0-4)[d]			
0	49 (20%)	18 (15%)	67 (18%)
1	149 (59%)	70 (57%)	219 (58%)
2	43 (17%)	31 (25%)	74 (20%)
3	10 (4%)	5 (4%)	15 (4%)
Mean±SD	1.1±0.72	1.2±0.73	1.1±0.73
Median	1.0	1.0	1.0
Range	0.0-3.0	0.0-3.0	0.0-3.0

[a] A prospective stratification into tumor type (hematological or solid) and hemoglobin level (≤10.5 g/dL or >10.5 g/dL) was applied in order to maintain the 2:1 ratio of epoetin alfa subjects to placebo subjects in these strata.

[b] Includes non-Hodgkin's and Hodgkin's lymphoma.

[c] For calculation of months since diagnosis: dates with known year but unknown month, the unknown month was interpreted as 6; and dates with known year and known month but unknown day, the unknown day was interpreted as 15.

[d] ECOG performance scores: 0 = able to carry out all normal activity without restriction; 1 = restricted in physically strenuous activity but ambulatory and able to do light work; 2 = ambulatory and capable of all self-care but unable to carry out any work; 3 = capable of only limited self-care, confined to bed or chair more than 50% of waking hours; 4 = completely disabled; cannot carry out any self care; totally confined to bed or chair.

In the intent-to-treat population, the baseline characteristics of history and extent of malignancy (Tables 3 and 4), ECOG performance scores (Table 3), and mean laboratory values (Table 5) were generally comparable between the two treatment groups. For all subjects, the median time since subjects were diagnosed with a malignancy was 17 months. Primary bone marrow involvement was present in 28% of all subjects and metastatic bone marrow involvement was present in 15% of all subjects. As shown in Table 4, the most common types of malignancies overall were breast (30%), non-Hodgkin's lymphoma (17%), and myeloma (17%).

Table 4: Diagnosis of Malignancy (Intent-to-Treat Population)

Diagnosis	Epoetin Alfa (N=251)	Placebo (N=124)	Overall (N=375)
Breast	78 (31%)	36 (29%)	114 (30%)
Non-Hodgkin's lymphoma	41 (16%)	21 (17%)	62 (17%)
Myeloma	37 (15%)	25 (20%)	62 (17%)
Hodgkin's lymphoma	19 (8%)	6 (5%)	25 (7%)
Chronic lymphatic leukemia	16 (6%)	5 (4%)	21 (6%)
Gastrointestinal[a]	17 (7%)	4 (3%)	21 (6%)
Ovarian	10 (4%)	7 (6%)	17 (5%)
Other[b]	10 (4%)	6 (5%)	16 (4%)
Lung	10 (4%)	3 (2%)	13 (4%)
Pancreas	5 (2%)	2 (2%)	7 (2%)
Prostate	4 (2%)	3 (2%)	7 (2%)
Sarcoma	2 (1%)	5 (4%)	7 (2%)
Unknown[c]	2 (1%)	1 (1%)	3 (1%)

[a] Of the 21 subjects who had a gastrointestinal malignancy, 16 had a colon (8 epoetin alfa subjects, 4 placebo subjects), rectal (2 epoetin alfa subjects), or colorectal (2 epoetin alfa subjects) malignancy; 4 epoetin alfa subjects had a stomach malignancy and 1 epoetin alfa subject had an unknown gastrointestinal malignancy.
[b] Includes tumor types that occurred in fewer than 3 subjects overall.
[c] Malignancy of unknown primary origin.

Overall, 18% percent of the subjects had a baseline ECOG performance score of 0, indicating that they were able to carry out all normal activity without restriction; 58% of subjects had a baseline score of 1, indicating that they were restricted in physically strenuous activity but ambulatory and able to do light work; 20% of subjects had a baseline score of 2, indicating that they were ambulatory and capable of self-care but unable to carry out any work; and 4% of the subjects had a baseline score of 3, indicating that they

were capable of only limited self-care and were confined to bed or a chair more than 50% of their waking hours.

Table 5: Baseline Laboratory Values (Intent-to-Treat Population)

Characteristic	Epoetin Alfa (N=251)	Placebo (N=124)	Overall (N=375)
Hemoglobin (g/dL)			
Mean±SD	9.9±1.13	9.7±1.13	9.8±1.14
Median	9.9	9.7	9.8
Range	5.9-14.3	6.6-12.7	5.9-14.3
Hematocrit (%)	(N=250)	(N=123)	(N=373)
Mean±SD	30.4±3.45	29.7±3.54	30.2±3.49
Median	30.1	29.6	30.0
Range	18.0-42.0	21.0-41.0	18.0-42.0
Red blood cell count ($x10^{12}$/L)	(N=249)	(N=123)	(N=372)
Mean±SD	3.4±0.54	3.2±0.53	3.3±0.54
Reticulocyte count (%)	(N=243)	(N=123)	(N=366)
Mean±SD	2.2±1.31	2.3±1.50	2.3±1.38
Median	2.0	2.0	2.0
Range	0.0-7.5	0.0-11.5	0.0-11.5
Reticulocyte count (%) assessed automatically	(N=175)	(N=90)	(N=265)
Mean±SD	2.3±1.33	2.3±1.56	2.3±1.41
Median	2.2	2.0	2.1
Range	0.0-7.5	0.0-11.5	0.0-11.5
White blood cell count ($x10^9$/L)			
Mean±SD	8.6±21.32	9.1±21.48	8.8±21.35
Neutrophil count (%)	(N=246)	(N=122)	(N=368)
Mean±SD	62.2±20.58	63.0±20.64	62.5±20.57
Median	66.0	67.8	67.4
Range	1.0-96.0	1.0-96.0	1.0-96.0
Absolute neutrophil count ($x10^9$/L)	(N=246)	(N=122)	(N=368)
Mean±SD	3.83±3.14	3.66±2.65	3.78±2.98
Median	2.93	3.06	3.00
Range	0.10-21.89	0.07-15.55	0.07-21.89
Serum erythropoietin (mU/mL)	(N=233)	(N=117)	(N=350)
Mean±SD	103±192.7	91±103.1	99±168.1
Median	50	51	50
Range	10-1890	10-597	10-1890

Baseline laboratory values were comparable between groups. Since the automatic assessment of reticulocyte counts is known to be more reliable than manual assessment, summaries of reticulocyte counts assessed only by automatic means are provided in this report in addition to reticulocyte counts assessed by either manual or automatic means.

In general, the incidence of medical history and baseline physical examination abnormalities were similar between the two treatment groups.

Prestudy transfusion patterns are summarized in Table 6. Subjects who had received at least one transfusion during the three months before study entry

(i.e., during the 84 days before Day 1) were referred to as baseline transfusion dependent. Overall, more than two-thirds (69%) of the subjects were not transfusion dependent at baseline. Of those subjects who were transfusion dependent at baseline, the percentage was lower in the epoetin alfa group (28%) than in the placebo group (36%). This imbalance in baseline transfusion dependence was taken into account during the analysis of the primary efficacy variable. Of the subjects who were transfusion dependent at baseline, subjects in the epoetin alfa group received a mean of 3.5 units per three months prestudy and subjects in the placebo group received a mean of 2.7 units per three months prestudy. The mean hemoglobin at the time of transfusion for subjects who were transfusion dependent at baseline was 8.2 g/dL for the epoetin alfa group and 8.1 g/dL for the placebo group.

Table 6: Prestudy Transfusion Patterns (Intent-to-Treat Population)

Transfusion Pattern	Epoetin Alfa (N=251)	Placebo (N=124)	Overall (N=375)
Transfusion-dependent at baseline	71 (28%)	44 (36%)	115 (31%)
Prestudy transfusion rate (units/3 months) (all subjects)	(N=251)	(N=122)	(N=373)
Mean±SD	1.0±2.03	0.9±1.51	1.0±1.87
Median	0.0	0.0	0.0
Range	0.0-13.0	0.0-8.0	0.0-13.0
Prestudy transfusion rate (units/3 months) (subjects transfusion dependent at baseline)	(N=71)	(N=42)	(N=113)
Mean±SD	3.5±2.44	2.7±1.41	3.2±2.15
Median	2.0	2.0	2.0
Range	1.0-13.0	1.0-8.0	1.0-13.0
Mean hemoglobin (g/dL) at time of transfusion (subjects transfusion dependent at baseline)[a]			
Mean±SD	(N=70)	(N=42)	(N=112)
Median	8.2±0.91	8.1±1.11	8.2±0.99
Range	8.3	8.2	8.2
	6.1-9.8	5.5-10.8	5.5-10.8

[a] Excluding hemoglobin values within 14 days after a transfusion.

Study Completion/Withdrawal Information

Information on completion of and discontinuation from the study is presented in Table 7. Subjects completed the study if they completed study medication administration as described in Dosage and Administration, and had all evaluations completed at appropriate visits including study termination. The intent-to-treat population included 251 subjects treated with epoetin alfa and

124 treated with placebo. Seven (3%) subjects in the epoetin alfa group and nine (7%) subjects in the placebo group were not evaluable for efficacy. As per the protocol, the efficacy population included subjects who were randomly assigned to a treatment group and were in the study for more than 28 days. Six (2%) subjects in the epoetin alfa and eight (6%) subjects in the placebo group were discontinued from the study within the first 28 days on study. Of these subjects, three epoetin alfa-treated subjects and five placebo-treated subjects discontinued because of adverse events, death, or disease progression. In addition to the 14 subjects who discontinued on or before Day 28, one subject in each of the epoetin alfa (3129) and placebo (3127) groups was excluded from the efficacy population because the blind was prematurely broken on their treatment codes; both of these subjects completed the study. In the intent-to-treat population, 77% of epoetin alfa-treated subjects and 72% of placebo-treated subjects were still in the trial at the initiation of Week 12; 57% of epoetin alfa-treated subjects and 42% of placebo-treated subjects were still in the trial at the initiation of Week 16. Overall, 97% (244) of 251 epoetin alfa subjects and 93% (115) of 124 placebo subjects were evaluable for efficacy.

Table 7: Completion and Discontinuation Information

	Epoetin Alfa (N=251)	Placebo (N=124)	Overall (N=375)
Intent-to-treat population	251 (100%)	124 (100%)	375 (100%)
Completed	155 (62%)	61 (49%)	216 (58%)
Not evaluable for efficacy	7 (3%)	9 (7%)	16 (4%)
Discontinued ≤28 days on study	6 (2%)	8 (6%)	14 (4%)
Subject choice	2	2	4
Other[a]	3	6	9
Death	1	3	4
Disease progression	1	2	3
Adverse event	1	0	1
All others	0	1	1
Lost to follow-up	1	0	1
Blind broken on treatment code[b]	1	1	2
Efficacy evaluable population	244 (97%)	115 (93%)	359 (96%)
Completed	154 (63%)	60 (52%)	214 (60%)
Discontinued >28 days on study	90 (37%)	55 (48%)	145 (40%)
Subject choice	16	18	34
Other[a]	70	37	107
Death	16	11	27
Disease progression	18	9	27
Stop or change in chemotherapy	19	7	26
Adverse event	11	4	15
Absence of response	2	2	4
All others	4	4	8
Lost to follow-up	4	0	4
Safety population	251 (100%)	124 (100%)	375 (100%)

[a] Breakdown of categories under 'Other' was determined by the sponsor from the reason for discontinuation specified on the CRF by the investigator.

[b] For one subject in each of the two treatment groups, the blind was prematurely broken on their treatment code resulting in their exclusion from the efficacy population; both subjects completed the study.

The primary reasons for discontinuation after 28 days on study in the efficacy population for both treatment groups were subject choice, death, disease progression, and a change or stop of chemotherapy.

All subjects that were included in the intent-to-treat population were also included in the safety population.

Treatment Compliance

There was generally good compliance with the dosage schedule except for those subjects who discontinued prematurely. The following subjects had

protocol deviations regarding study drug administration. These data were derived from source monitoring and are not reported in the data listings.

Subject 2105 (placebo group) was mistakenly given the study medication for subject 1157 (placebo group) at the Week 2 visit and used this medication for the study injections given on Days 14, 17, 19, 21, 24, and 26. For the remaining study period, subject 2105 used the correct study drug.

Subject 4070 (epoetin alfa group) was mistakenly given study drug labeled for subject 4030 (placebo group) for a period of two weeks from Week 2 to Week 4. After Week 4, the correct study drug was again given to subject 4070 and the subject continued on the study.

Concomitant Therapies

In the intent-to-treat population, the percentage of subjects who used concomitant therapy on study was similar for the epoetin alfa (94%) and placebo (96%) groups. The most frequent concomitant medications used on study are listed in Table 8. In general, the frequency of concomitant therapy use was comparable between the two treatment groups. Over 50% of the subjects in both treatment groups received antianemic preparations while on study; the majority of these antianemic preparations were iron (ferrous) salts. Three epoetin alfa-treated subjects (1008, 1081, and 3053) and two placebo-treated subjects (1105 and 4052) received i.v. iron supplementation while on study. The reasons given for i.v. iron supplementation were "low transferrin saturation" (1008 and 1081) and "iron deficiency" (1008, 3053, 1105, and 4052). Three subjects (two in the epoetin alfa group and one in the placebo group) received vitamin B_{12} supplementation. The frequency and types of concomitant medications used on study were not unexpected for the subject population participating in this study.

Table 8: Most Frequent (≥10% Overall) Concomitant Therapies Used On Study (Intent-to-Treat Population)

Therapeutic Class Pharmacologic Class	Epoetin Alfa (N=251)	Placebo (N=124)	Overall (N=375)
Any concomitant therapy	**236 (94%)**	**119 (96%)**	**355 (95%)**
Alimentary tract and metabolism	**194 (77%)**	**95 (77%)**	**289 (77%)**
Antiemetics and antinauseants	117 (47%)	42 (34%)	159 (42%)
Antacids, drugs for treatment of peptic ulcer	82 (33%)	33 (27%)	115 (31%)
Antiplasmodic and anticholinergic agents	74 (29%)	37 (30%)	111 (30%)
Stomatologicals, mouth preparations	74 (29%)	33 (27%)	107 (29%)
Antidiarrheals, intestinal anti-inflammatories/ anti-infectives	62 (25%)	38 (31%)	100 (27%)
Laxatives	34 (14%)	17 (14%)	51 (14%)
Mineral supplements	26 (10%)	18 (15%)	44 (12%)
Blood and blood forming organs	**158 (63%)**	**85 (69%)**	**243 (65%)**
Antianemic preparations	144 (57%)	76 (61%)	220 (59%)
Antithrombotic agents	28 (11%)	14 (11%)	42 (11%)
Nervous system	**106 (42%)**	**55 (44%)**	**161 (43%)**
Analgesics	85 (34%)	44 (35%)	129 (34%)
Psycholeptics	50 (20%)	23 (19%)	73 (19%)
General anti-infectives for systemic use	**106 (42%)**	**52 (42%)**	**158 (42%)**
Antibacterials for systemic use	104 (41%)	47 (38%)	151 (40%)
Antineoplastic and immunosuppressive agents	**75 (30%)**	**31 (25%)**	**106 (28%)**
Immunomodulating agents[a]	67 (27%)	28 (23%)	95 (25%)
Cardiovascular system	**68 (27%)**	**37 (30%)**	**105 (28%)**
Diuretics	42 (17%)	27 (22%)	69 (18%)
Cardiac therapy	28 (11%)	13 (10%)	41 (11%)
Musculoskeletal system	**62 (25%)**	**38 (31%)**	**100 (27%)**
Drugs for the treatment of bone disease	35 (14%)	21 (17%)	56 (15%)
Antiinflammatory and antirheumetics	22 (9%)	15 (12%)	37 (10%)
Dermatologicals	**62 (25%)**	**27 (22%)**	**89 (24%)**
Antibiotics and chemotherapeutics, dermatologicals	28 (11%)	12 (10%)	40 (11%)
Respiratory system	**54 (22%)**	**28 (23%)**	**82 (22%)**
Cough and cold preparations	35 (14%)	18 (15%)	53 (14%)
Genitourinary system and sex hormones	**43 (17%)**	**17 (14%)**	**60 (16%)**

[a] The most frequently used immunomodulating agents included filgrastim and lenograstim.

Chemotherapies

Overall, the most frequent chemotherapeutic agents used on study were cyclophosphamide (33%), doxorubicin (24%), vincristine (20%), and fluorouracil (18%). For the most common tumor types enrolled in the study (breast, non-Hodgkin's lymphoma, myeloma, Hodgkin's lymphoma, chronic lymphocytic leukemia, and gastrointestinal), the most frequent chemotherapeutic agents used on study are listed in Table 9. There were some differences between the treatment groups in on-study use of chemotherapeutic agents; however, these differences can be attributed to the small number of subjects who received each type of drug.

Table 9: Most Frequent (≥20% Overall) Chemotherapeutic Agents Used On Study by Tumor Type (Intent-to-Treat Population)

Diagnosis of Malignancy Chemotherapeutic Agent[a]	Epoetin Alfa (N=251)	Placebo (N=124)	Overall (N=375)
Breast	**(N=78)**	**(N=36)**	**(N=114)**
Cyclophosphamide	35 (44.9%)	13 (36.1%)	48 (42.1%)
Fluorouracil	31 (39.7%)	16 (44.4%)	47 (41.2%)
Epirubicin	21 (26.9%)	8 (22.2%)	29 (25.4%)
Methotrexate	14 (18.0%)	9 (25.0%)	23 (20.2%)
Non-Hodgkin's Lymphoma	**(N=41)**	**(N=21)**	**(N= 62)**
Cyclophosphamide	26 (63.4%)	11 (52.4%)	37 (59.7%)
Vincristine	24 (58.5%)	9 (42.9%)	33 (53.2%)
Doxorubicin	22 (53.7%)	5 (23.8%)	27 (43.6%)
Myeloma	**(N=37)**	**(N=25)**	**(N=62)**
Melphalan	21 (56.8%)	13 (52.0%)	34 (54.8%)
Vincristine	11 (29.7%)	5 (20.0%)	16 (25.8%)
Doxorubicin	12 (32.4%)	4 (16.0%)	16 (25.8%)
Cyclophosphamide	6 (16.2%)	8 (32.0%)	14 (22.6%)
Hodgkin's Lymphoma	**(N=19)**	**(N=6)**	**(N=25)**
Bleomycin	14 (73.7%)	4 (66.7%)	18 (72.0%)
Doxorubicin	12 (63.2%)	4 (66.7%)	16 (64.0%)
Etoposide	12 (63.2%)	2 (33.3%)	14 (56.0%)
Vincristine	9 (47.4%)	4 (66.7%)	13 (52.0%)
Cyclophosphamide	4 (21.1%)	1 (16.7%)	5 (20.0%)
Chronic Lymphatic Leukemia	**(N=16)**	**(N=5)**	**(N=21)**
Cyclophosphamide	7 (43.8%)	1 (20.0%)	8 (38.1%)
Vincristine	5 (31.3%)	1 (20.0%)	6 (28.6%)
Gastrointestinal	**(N=17)**	**(N=4)**	**(N=21)**
Fluorouracil	13 (76.5%)	3 (75.0%)	16 (76.2%)

[a] Some subjects received more than one chemotherapeutic agent in combination.

For the intent-to-treat population, the mean number of chemotherapy cycles on study was comparable between the two treatment groups (3.8±1.52 cycles for epoetin alfa-treated subjects and 3.4±1.61 cycles for placebo-treated subjects). One hundred ninety-seven (78%) of 251 epoetin alfa-treated subjects and 86 (69%) of 124 placebo-treated subjects received at least three chemotherapy cycles during the course of the study.

As shown in Table 10 for the intent-to-treat population, the mean weekly absolute neutrophil count was similar between the two treatment groups and there was no statistically significant difference (p=0.92) between the treatment groups in mean area under the curve indicating similar intensity of chemotherapy between the two groups over the course of the study. For the efficacy population, there was also no statistically significant difference

(p=1.00) between the treatment groups in mean area under the curve for absolute neutrophil count.

Table 10: Area Under the Curve of the Weekly Absolute Neutrophil Count ($x10^9/L$) (Intent-to-Treat Population)

	Epoetin Alfa (N=251)			Placebo (N=124)			Overall (N=375)		
Week	N	Mean	SD	N	Mean	SD	N	Mean	SD
0	232	3.69	2.890	113	3.73	2.689	345	3.70	2.822
1	246	3.75	2.994	122	3.66	2.648	368	3.72	2.881
2	247	3.22	2.968	122	3.38	3.997	369	3.28	3.339
3	251	3.03	3.401	124	3.25	4.014	375	3.10	3.612
4	251	3.53	3.244	124	3.56	3.897	375	3.54	3.469
5	251	3.18	2.993	124	3.31	3.797	375	3.22	3.276
6	251	3.22	3.241	124	3.48	3.981	375	3.31	3.500
7	251	3.17	3.205	124	3.48	4.120	375	3.28	3.532
8	251	3.33	3.139	124	3.16	3.959	375	3.27	3.428
9	251	3.31	2.850	124	3.45	4.394	375	3.36	3.433
10	251	3.22	2.868	124	3.59	4.696	375	3.34	3.575
11	251	3.50	4.027	124	3.56	4.629	375	3.52	4.230
12	251	3.62	3.952	124	3.63	4.776	375	3.63	4.236
13	251	3.79	3.956	124	3.73	4.718	375	3.77	4.217
14	251	3.70	3.945	124	3.75	4.684	375	3.71	4.198
15	251	3.72	3.929	124	3.82	4.657	375	3.76	4.178
16	251	3.92	4.019	124	3.79	4.668	375	3.87	4.239
17	251	3.95	4.013	124	3.94	4.617	375	3.95	4.216
18	251	4.02	4.360	124	3.81	4.629	375	3.95	4.446
19	251	4.01	4.325	124	3.69	4.662	375	3.91	4.436
20	251	4.14	4.401	124	3.78	4.632	375	4.03	4.475
21	251	4.21	4.432	124	3.89	4.618	375	4.11	4.491
22	251	4.17	4.350	124	3.82	4.628	375	4.05	4.441
23	251	4.16	4.337	124	3.80	4.623	375	4.04	4.431
24	251	4.18	4.289	124	3.90	4.614	375	4.09	4.395
*Area under curve	251	87.94	67.770	124	87.14	93.897	375	87.68	77.264

NOTE: Missing values on study were substituted with previous observation up to Week 24.
* Area under the curve: p-value (t-test)=0.92.

Protocol Deviations

Protocol deviations that were reported in the investigator's general eligibility statement required permission from the sponsor before enrolling the subject in the study.

In general, the proportion of subjects who deviated from the protocol was similar between the two treatment groups. The most frequent protocol deviations were deviations from inclusion/exclusion criteria. The most frequent inclusion/exclusion criteria deviations (12% of epoetin alfa subjects; 11% of placebo subjects) were related to the requirement that laboratory values be within protocol-specified limits after recovery from the previous

chemotherapy cycle. In addition, 19 (5% of subjects in each of the two treatment groups) subjects did not have their baseline hemoglobin value measured within the seven days before study entry. For these 19 subjects, the day the baseline hemoglobin was measured ranged from 9 to 22 days before study entry. Five (1% of epoetin alfa subjects; 2% of placebo subjects) subjects received platinum-containing chemotherapy while on study and 4 (1% of epoetin alfa subjects; 2% of placebo subjects) subjects had protocol deviations related to study drug administration.

Efficacy Results

DATA SET ANALYZED

The primary efficacy variable was an analysis of the proportion of subjects transfused after Day 28 up to study completion. For this variable, analyses of both the intent-to-treat and efficacy populations were performed and are presented in this section. For the secondary efficacy variables, analyses of the efficacy population were performed and are presented.

DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Three hundred fifty-nine subjects enrolled at 72 sites in 15 countries were included in the efficacy population. Approximately half of the subjects were enrolled in Germany (21%), the Netherlands (16%), and Great Britain (11%). Two hundred forty-four subjects were randomly assigned to receive epoetin alfa and 115 subjects were randomly assigned to receive placebo.

In the efficacy population, demographic characteristics were generally comparable between the epoetin alfa and placebo treatment groups. For all subjects, mean age was 58.8 years, mean weight was 67.6 kg, and mean height was 166 cm. There were twice as many women (67%) enrolled as men (33%) and the majority (96%) of subjects were of white racial origin.

Overall, solid tumors were present in 54% of the subjects and hematological tumors (included non-Hodgkin's and Hodgkin's lymphoma) in 47% of subjects. Eighty-four percent of all the subjects were stratified to a hemoglobin $\leq$10.5 g/dL and 16% were stratified to a hemoglobin >10.5 g/dL.

In the efficacy population, the baseline characteristics of history and extent of malignancy, ECOG performance scores, and mean laboratory values were generally comparable between the two treatment groups. Overall, the median time since subjects were diagnosed with a malignancy was 17 months. Primary bone marrow involvement was present in 28% of all subjects and metastatic bone marrow involvement was present in 15% of all subjects. The most common types of malignancies overall were breast (31%), non-Hodgkin's lymphoma (17%), and myeloma (16%).

Overall, 18% of the subjects had a baseline ECOG performance score of 0, indicating that they were able to carry out all normal activity without restriction; 59% of subjects had a baseline score of 1, indicating that they were restricted in physically strenuous activity but ambulatory and able to do light work; 18% of subjects had a baseline score of 2, indicating that they were ambulatory and capable of self-care but unable to carry out any work; and 4% of the subjects had a baseline score of 3, indicating that they were capable of only limited self-care and were confined to bed or a chair more than 50% of their waking hours.

Overall, baseline mean values for hemoglobin, hematocrit, reticulocyte count (assessed manually or automatically), reticulocyte count (assessed automatically), absolute neutrophil count, and serum erythropoietin were 9.9 g/dL, 30%, 2%, 2%, 3.76 x10^9/L, and 98 mU/mL, respectively.

In general, the incidence of medical history abnormalities and baseline physical examination abnormalities were similar between the two treatment groups.

More than two-thirds (69%) of the subjects were not transfusion dependent at baseline. Of those subjects who were transfusion dependent (received at least one transfusion during the three months before study entry) at baseline, the percentage was lower in the epoetin alfa group (29%) than in the placebo group (34%). Of the subjects who were transfusion dependent at baseline, subjects in the epoetin alfa group received a mean of 3.5 units per three months prestudy and subjects in the placebo group received a mean of 2.5 units per three months prestudy. The mean hemoglobin at the time of

transfusion for subjects who were transfusion dependent at baseline was 8.2 g/dL for both the epoetin alfa and placebo groups.

SUMMARY OF EACH EFFICACY MEASURE

Primary Efficacy Variable: Proportion of Subjects Transfused After Day 28

The intent-to-treat analysis of the primary efficacy variable was planned as the main analysis of the study. For the intent-to-treat analysis, subjects who were on study for 28 days or less were counted as transfused. The proportion of subjects transfused after day 28 by treatment group is shown in Table 11. In the intent-to-treat population, the proportion of subjects transfused after Day 28 was lower in the epoetin alfa group (24.7%) than in the placebo group (39.5%). The logistic regression results with randomized treatment group, tumor type, and hemoglobin stratum as covariates showed that the effect of randomized treatment group on the proportion of subjects transfused after Day 28 was statistically significant (p=0.0057). The results were similar for the efficacy population with the proportion of subjects transfused after Day 28 being significantly lower (p=0.0168) in the epoetin alfa group (23.0%) compared with the placebo group (35.7%). Since for the intent-to-treat population, subjects who were on study for 28 days or less were counted as transfused, the fact that the treatment effect is still statistically significant for the efficacy population indicates that the applied model is robust against effects caused by the different proportion of subjects who discontinued early in the two treatment groups

Table 11: Proportion of Subjects Transfused After Day 28 (Intent-to-Treat and Efficacy Populations)

Population	Epoetin Alfa	Placebo	p value[a]
Intent-to-Treat Population	(N=251)	(N=124)	
	62 (24.7%)	49 (39.5%)	0.0057
Efficacy Population	(N=244)	(N=115)	
	56 (23.0%)	41 (35.7%)	0.0168

[a] Wald Chi-Square test from logistic model correcting for tumor type and hemoglobin stratum.

The proportion of subjects transfused after Day 28 by the stratifications of tumor type (solid or hematological) and hemoglobin level (≤10.5 g/dL or >10.5 g/dL) is shown in Table 12. Regardless of the tumor type or hemoglobin level, the proportion of subjects transfused after Day 28 was greater in the placebo group than in the epoetin alfa group. The logistic regression results with treatment group, tumor type, and hemoglobin stratum as covariates showed that the relationship between tumor type and the proportion of subjects transfused after Day 28 was not statistically significant for either the intent-to-treat (p=0.43) or efficacy (p=0.19) populations. The effect of hemoglobin stratum as a covariate was statistically significant for both the intent-to-treat (p=0.0017) and efficacy (p=0.0022) populations.

Since fewer epoetin alfa-treated subjects than placebo-treated subjects were transfusion-dependent at baseline, an additional logistic regression analysis was performed to correct for baseline transfusion dependence as well as tumor type and hemoglobin stratum. The difference between the randomized treatment groups in proportion of subjects transfused after Day 28 remained statistically significant for both the intent-to-treat (p=0.0114) and efficacy (p=0.0232) populations. The predictive value of baseline transfusion dependence for the proportion of subjects transfused after Day 28 was also statistically significant (p=0.0001 for both populations) in these models.

Table 12: Proportion of Subjects Transfused After Day 28 by Subgroup (Intent-to-Treat and Efficacy Populations)

Subgroup	Epoetin Alfa		Placebo	
Intent-to-Treat Population	(N=251)		(N=124)	
Tumor Type				
Solid	33/136	(24.3%)	24/66	(36.4%)
Hematological	29/115	(25.2%)	25/58	(43.1%)
Hemoglobin Stratum				
≤10.5 g/dL	59/209	(28.2%)	46/109	(42.2%)
>10.5 g/dL	3/42	(7.1%)	3/15	(20.0%)
Efficacy Population	(N=244)		(N=115)	
Tumor Type				
Solid	28/131	(21.4%)	19/61	(31.1%)
Hematological	28/113	(24.8%)	22/54	(40.7%)
Hemoglobin Stratum				
≤10.5 g/dL	54/203	(26.6%)	38/100	(38.0%)
>10.5 g/dL	2/41	(4.9%)	3/15	(20.0%)

Secondary Efficacy Variables

Transfusion-R lated Variables

Proportion of Subjects Transfused or with a Hemoglobin Level Below 8 g/dL After Day 28. Since transfusions were given at the discretion of the investigator, any subject whose hemoglobin level fell below 8 g/dL and was not transfused was considered to have been transfused for the purpose of the efficacy analysis. Therefore, the efficacy analysis of proportion of subjects transfused or with a hemoglobin below 8 g/dL was performed to confirm the intent-to-treat analysis of the primary efficacy variable and to account for the variability among investigators in hemoglobin level at time of transfusion.

In the efficacy population, the proportion of subjects transfused or with a hemoglobin level below 8 g/dL after Day 28 was lower in the epoetin alfa group (25.0%) than in the placebo group (45.2%) (Table 13). The logistic regression results with randomized treatment group, tumor type, and hemoglobin stratum as covariates showed that the effect of randomized treatment group on the proportion of subjects transfused or with a hemoglobin below 8 g/dL after Day 28 was statistically significant (p=0.0002).

Regardless of tumor type (solid or hematological), hemoglobin stratum (≤10.5 g/dL or >10.5 g/dL), or baseline transfusion dependence, the proportion of subjects transfused or with a hemoglobin level below 8 g/dL after Day 28 was greater in the placebo group than in the epoetin alfa group. The logistic regression results with treatment group, tumor type, and hemoglobin stratum as covariates showed that the relationship between tumor type and the proportion of subjects transfused or with a hemoglobin level below 8 g/dL after Day 28 was not statistically significant (p=0.0999); the effect of hemoglobin stratum as a covariate was statistically significant (p=0.0007).

The proportion of subjects transfused or with a hemoglobin below 8 g/dL by month on study was consistently lower in the epoetin alfa group compared with the placebo group for Months 1 through 6; for Months 7 and 8, the proportion was higher in the epoetin alfa group compared with the placebo

group; however, the number of subjects on study at the end of these two months in both treatment groups was small.

Table 13: Proportion of Subjects Transfused or with Hemoglobin <8 g/dL After Day 28 by Subgroup and Month On Study (Efficacy Population)

Subgroup	Epoetin Alfa (N=244)		Placebo (N=115)		p value[a]
Overall	61	(25.0%)	52	(45.2%)	0.0002
Tumor Type					
Solid	29/131	(22.1%)	25/61	(41.0%)	
Hematological	32/113	(28.3%)	27/54	(50.0%)	
Hemoglobin Stratum					
≤10.5 g/dL	59/203	(29.1%)	48/100	(48.0%)	
>10.5 g/dL	2/41	(4.9%)	4/15	(26.7%)	
Baseline Transfusion Dependence					
No	33/173	(19.1%)	24/76	(31.6%)	
Yes	28/71	(39.4%)	28/39	(71.8%)	
Month On Study[b]					
1	48/244	(19.7%)	30/115	(26.1%)	
2	37/222	(16.7%)	34/104	(32.7%)	
3	21/181	(11.6%)	26/78	(33.3%)	
4	15/131	(11.5%)	15/45	(33.3%)	
5	7/84	(8.3%)	8/29	(27.6%)	
6	2/48	(4.2%)	7/14	(50.0%)	
7	2/16	(12.5%)	0/8	(0.0%)	
8	2/7	(28.6%)	0/2	(0.0%)	

[a] Wald Chi-Square test from logistic regression model correcting for tumor type and hemoglobin stratum.

[b] Denominator is the number of subjects on study at the end of each study month.

Of the subjects who were transfusion dependent at baseline, 60.6% (43/71) of subjects in the epoetin alfa group compared with 28.2% (11/39) of subjects in the placebo group became transfusion independent after Day 28 (i.e., not transfused or no hemoglobin below 8 g/dL after Day 28) (Table 14). Of the subjects who were transfusion independent at baseline, 19.1% (33/173) of subjects in the epoetin alfa group compared with 31.6% (24/76) of subjects in the placebo group became transfusion dependent after Day 28 (i.e., transfused or with a hemoglobin below 8 g/dL after Day 28).

Table 14: Proportion of Subjects Who Became Transfusion Independent or Transfusion Dependent After Day 28 (Efficacy Population)

	Epoetin Alfa (N=244)	Placebo (N=115)
Baseline Transfusion Dependent		
No	173 (70.9%)	76 (66.1%)
Yes	71 (29.1%)	39 (33.9%)
Transfusion dependent at baseline and became transfusion independent after Day 28 (not transfused or no hemoglobin below 8 g/dL after Day 28)	(N=71) 43 (60.6%)	(N=39) 11 (28.2%)
Transfusion independent at baseline and became transfusion dependent after Day 28 (transfused or with hemoglobin below 8 g/dL after Day 28)	(N=173) 33 (19.1%)	(N=76) 24 (31.6%)

Cumulative Transfusion Rate. Cumulative transfusion rate was calculated as the number of units transfused per subject per three months on study. Transfusions after Day 28 up until study end were evaluated.

In the efficacy population, 29.1% of subjects in the epoetin alfa group and 33.9% of subjects in the placebo group were transfusion dependent at baseline. The median baseline transfusion rate for subjects who were transfusion dependent at baseline was 2.0 units per three months prior to study for both the epoetin alfa and placebo groups (Table 15). For all subjects who were transfused after Day 28, the median cumulative transfusion rate was lower in the epoetin alfa group (3.8 units per three months on study) than in the placebo group (4.7 units per three months on study). For subjects who were transfusion independent at baseline and who became transfusion dependent on study, the median cumulative transfusion rate after Day 28 was approximately one and one-half times lower in the epoetin alfa group (3.8 units per three months on study) than in the placebo group (5.2 units per three months on study). For subjects who were transfusion dependent at baseline and who remained transfusion dependent on study, the median cumulative transfusion rate after Day 28 was also lower in the epoetin alfa group (3.8 units per three months on study) than in the placebo group (4.6 units per three months on study).

Table 15: Cumulative Transfusion Rate After Day 28 (Efficacy Population)

Variable (Population)	Epoetin Alfa (N=244)	Placebo (N=115)
Baseline transfusion rate (units/3 months prestudy) (subjects transfusion dependent at baseline)	(N=71)	(N=37)[a]
Mean±SD	3.5±2.44	2.5±1.10
Median	2.0	2.0
Range	1.0-13.0	1.0-6.0
Cumulative transfusion rate (units/3 months on study) (all subjects transfused after Day 28)	(N=56)	(N=40)
Mean±SD	6.1±6.53	7.1±7.55
Median	3.8	4.7
Range	0.8-33.6	1.6-42.0
Cumulative transfusion rate (units/3 months on study) (subjects transfusion independent at baseline and transfused after Day 28)	(N=29)	(N=16)
Mean±SD	4.9±4.27	8.3±10.00
Median	3.8	5.2
Range	1.0-20.0	1.6-42.0
Cumulative transfusion rate (units/3 months on study) (subjects transfusion dependent at baseline and transfused after Day 28)	(N=27)	(N=24)
Mean±SD	7.4±8.20	6.3±5.46
Median	3.8	4.6
Range	0.8-33.6	2.4-25.8

[a] The number of units transfused were unavailable for two placebo-treated subjects who were transfusion-dependent at baseline, therefore there are 37 transfusion-dependent placebo subjects at baseline (two less than in Table 14).

Time to First Transfusion or a Hemoglobin Level Below 8 g/dL After Day 28. The time to first transfusion or hemoglobin level below 8 g/dL after Day 28 is shown in Figure 1. As shown in the figure, the time to first transfusion requirement after Day 28 was significantly (p=0.0001) longer for subjects in the epoetin alfa group than for subjects in the placebo group. At Week 16, the probability of no transfusion requirement (Kaplan-Meier estimate) was 75% in the epoetin alfa group and 55% in the placebo group.

Mean pretransfusion hemoglobin levels. In the intent-to-treat population, the mean hemoglobin level at the time of transfusion (excluding hemoglobin values within 14 days after a transfusion) was similar for the epoetin alfa (7.9 g/dL) and placebo (7.8 g/dL) groups (Table 16). The mean

pretransfusion hemoglobin levels were also similar for the epoetin alfa and placebo groups regardless of whether the subjects were transfusion dependent (8.0 g/dL and 7.6 g/dL, respectively) or transfusion independent (7.8 g/dL and 8.0 g/dL, respectively) at baseline. These low transfusion triggers indicate that, although the decision of transfusion was left up to the discretion of the investigators, the recommendation set forth in the protocol not to transfuse unless the hemoglobin decreased below 8 g/dL was generally adhered to by the investigators. For the efficacy population, the summary of mean hemoglobin level at the time of transfusion was similar to that described for the intent-to-treat population.

Table 16: Summary of Transfusion Independent Pretransfusion Hemoglobin Levels (g/dL) (Intent-to-Treat Population)

	Epoetin Alfa (N=251)	Placebo (N=124)
Mean hemoglobin (g/dL) at time of transfusion[a] (all subjects)		
N	72	56
Mean±SD	7.9±1.02	7.8±1.05
Median	8.0	7.8
Range	5.2-10.2	4.7-9.6
Mean hemoglobin (g/dL) at time of transfusion[a] (subjects transfusion-dependent at baseline)		
N	31	32
Mean±SD	8.0±1.09	7.6±1.08
Median	7.9	7.4
Range	5.2-10.2	4.7-9.6
Mean hemoglobin (g/dL) at time of transfusion[a] (subjects transfusion-independent at baseline)		
N	41	24
Mean±SD	7.8±0.98	8.0±0.98
Median	8.1	8.1
Range	5.4-9.5	5.5-9.5

[a] Ignoring hemoglobin values within 14 days after a transfusion

Changes in Hemoglobin Level, Hematocrit Level, and Reticulocyte Count

Hemoglobin levels rose a mean of 2.2 g/dL in the epoetin alfa group from baseline to last value compared with only a slight mean increase of 0.5 g/dL in the placebo group (Table 17 and Figure 2); the difference between the treatment groups was statistically significant ($p<0.001$). Similarly, hematocrit levels rose a mean of 7.3% in the epoetin alfa group over the course of the study compared with a mean increase of 1.1% in the placebo

group (Table 17 and Figure 3); the difference between the treatment groups was statistically significant ($p<0.001$). Transfusion-related hemoglobin and hematocrit values were not excluded from the calculation of mean changes. Therefore, even though subjects in the placebo group received more transfusions during the study than subjects in the epoetin alfa group, the mean increases in hemoglobin and hematocrit were still highly significantly greater in the epoetin alfa group compared with the placebo group.

There was also a greater mean increase from baseline to last value in reticulocyte counts (manually or automatically assessed) for the epoetin alfa group (0.5%) compared with the placebo group (0.1%). Because of the skewed distribution of the changes from baseline in reticulocyte counts, a non-parametric test was used to analyze the difference between the treatment groups; the difference between the treatment groups was statistically significant ($p=0.037$) (Table 17 and Figure 4). The similar results of both manual and automatic assessment of reticulocytes served as confirmation that manual results may be used.

Of particular importance when assessing the change in reticulocyte counts in relation to epoetin alfa treatment are the changes that occur within the first two to four weeks on study. At Week 0, mean reticulocyte counts (manually or automatically assessed) were similar for the epoetin alfa (2.2%) and placebo groups (2.4%). At Weeks 2 and 4 on study, there was essentially no change in mean reticulocyte counts for the placebo group (2.5% and 2.6%, respectively) compared with a mean increase for the epoetin alfa group (3.6% at both weeks). Similar changes were seen for reticulocyte counts that were only assessed automatically (Table 17; Figure 5).

Table 17: Change in Hemoglobin Level, Hematocrit Level, and Reticulocyte Count from Baseline to Last Value (Efficacy Population)

Variable Statistic	Epoetin Alfa (N=244)	Placebo (N=115)	p value[a]
Hemoglobin (g/dL)	(N=244)	(N=115)	<0.001
Mean±SD	2.2±2.18	0.5±1.79	
Median	2.1	0.5	
Range	-3.9-8.2	-3.7-7.9	
Hematocrit (%)	(N=243)	(N=114)	<0.001
Mean±SD	7.3±6.85	1.1±5.40	
Median	7.0	1.3	
Range	-10.9-25.0	-10.7-20.5	
Reticulocyte count (%)	(N=236)	(N=114)	0.037
Mean±SD	0.5±1.86	0.1±2.26	
Median	0.2	0.0	
Range	-5.0-7.6	-10.1-12.7	
Reticulocyte count (%) assessed automatically	(N=170)	(N=83)	0.321
Mean±SD	0.4±1.74	0.2±2.44	
Median	0.1	0.0	
Range	-5.0-6.7	-10.1-12.7	

NOTE: Transfusion-related values are not excluded from the calculation of mean changes.
[a] Used t-test for analysis of hemoglobin and hematocrit and Wilcoxon rank-sum test for analysis of reticulocyte count.

An evaluation of the change from baseline in hemoglobin and hematocrit levels by tumor type (solid or hematological) and hemoglobin stratum (≤10.5 g/dL or >10.5 g/dL) is presented in Table 18. The mean increases from baseline to last value in hemoglobin and hematocrit levels achieved by epoetin alfa-treated subjects for both tumor types were much higher than the mean changes observed by placebo-treated subjects. In addition, the mean increases from baseline seen within the epoetin alfa group were similar regardless of tumor type. For the three most representative tumor types (those occurring in at least 20 subjects in either treatment group) in this study (i.e., breast, non-Hodgkin's lymphoma, and myeloma), the mean increases from baseline to last value in hemoglobin and hematocrit levels were much higher in the epoetin alfa group than the placebo group. For the other tumor types represented in this study, no valuable statement can be made with regard to treatment comparisons because of the small number of subjects with each type of malignancy.

Table 18: Change in Hemoglobin and Hematocrit Levels from Baseline to Last Value by Tumor Type and Hemoglobin Stratum (Efficacy Population)

	Epoetin Alfa			Placebo		
	N	Mean	SEM	N	Mean	SEM

Hemoglobin (g/dL)		(N=244)			(N=115)	
Tumor type						
Solid	131	2.3	0.19	61	0.7	0.22
Hematological	113	2.2	0.21	54	0.3	0.25
Hemoglobin stratum						
≤10.5 g/dL	203	2.2	0.16	100	0.6	0.18
>10.5 g/dL	41	2.3	0.31	15	-0.4	0.39
Hematocrit (%)		(N=243)			(N=114)	
Tumor type						
Solid	130	7.8	0.61	61	1.6	0.67
Hematological	113	6.8	0.63	53	0.4	0.76
Hemoglobin stratum						
≤10.5 g/dL	202	7.3	0.49	99	1.5	0.54
>10.5 g/dL	41	7.7	0.96	15	-2.2	1.22

The mean increases from baseline to last value in hemoglobin and hematocrit levels achieved by epoetin alfa-treated subjects for both hemoglobin strata were much higher than the mean changes observed by placebo-treated subjects. In addition, the mean increases from baseline seen within the epoetin alfa group were similar regardless of hemoglobin strata. In the placebo group, subjects in the ≤10.5 g/dL hemoglobin stratum showed increases from baseline in hemoglobin and hematocrit levels compared with a decrease from baseline in hemoglobin and hematocrit for subjects in the >10.5 g/dL hemoglobin stratum; these differences are most likely related to the greater number of transfusions given to placebo subjects in the ≤10.5 g/dL stratum. Hemoglobin levels over the course of the study by hemoglobin stratum is presented graphically in Figure 6. Also shown in this figure, for subjects stratified to the >10.5 g/dL hemoglobin level, the mean hemoglobin levels were maintained or increased between Weeks 2 and 16 in the epoetin alfa group compared with the placebo group. (After Week 16, the number of subjects on study decreased making an assessment of treatment comparison less reliable.) This result supports that early treatment with epoetin alfa can prevent worsening anemia requiring transfusion.

Proportion of Responders and Correctors, and Final Response

The proportion of responders (subjects whose hemoglobin level increased by at least 2 g/dL during the study) and correctors (subjects who achieved a

hemoglobin level of at least 12 g/dL during the study), and final response (measured in four outcome categories) are presented in this section. Transfusion-related hemoglobin values on study were excluded from the determination of responders and correctors. The proportion of responders and correctors were calculated for subjects who were on study for at least 28 days. Final response was calculated for subjects who were on study for at least 56 days.

Proportion of Responders. Overall, there were significantly ($p<0.001$) more responders (70.5%) in the epoetin alfa group than in the placebo group (19.1%) (Table 19). This effect was maintained when an evaluation of the proportion of responders by tumor type (solid or hematological) and hemoglobin stratum (≤10.5 g/dL or >10.5 g/dL) was performed; the proportion of responders was greater in the epoetin alfa group than in the placebo group regardless of tumor type or hemoglobin stratum (Table 20). Within the epoetin alfa group, the proportion of responders was slightly greater in subjects with hematological vs. solid tumors, and in subjects in the higher vs. lower hemoglobin stratum.

Table 19: Proportion of Responders (Subjects Whose Hemoglobin Increased by ≥2 g/dL Unrelated to Transfusions) (Efficacy Population)

Response	Epoetin Alfa (N=244)	Placebo (N=115)	p value[a]
Responder	172 (70.5%)	22 (19.1%)	<0.001
Nonresponder	72 (29.5%)	93 (80.9%)	

[a] Fisher's Exact test.

Table 20: Proportion of Responders (Subjects Whose Hemoglobin Increased by ≥2 g/dL Unrelated to Transfusions) by Subgroup (Efficacy Population)

Subgroup	Epoetin Alfa (N=244)		Placebo (N=115)	
Tumor Type				
Solid	87/131	(66.4%)	13/61	(21.3%)
Hematological	85/113	(75.2%)	9/54	(16.7%)
Hemoglobin Stratum				
≤10.5 g/dL	139/203	(68.5%)	22/100	(22.0%)
>10.5 g/dL	33/41	(80.5%)	0/15	(0.0%)

Among the responders, the mean study day that they achieved a hemoglobin level that was at least 2 g/dL above baseline was reached earlier in the epoetin alfa group (52 days) compared with the placebo group (75 days) (Table 21). The maximum mean hemoglobin reached among the responders was higher in the epoetin alfa group (14.2 g/dL) than in the placebo group (12.2 g/dL).

Table 21: Summary of Responders (Subjects Whose Hemoglobin Increased by ≥2 g/dL Unrelated to Transfusions) (Responders in Efficacy Population)

	Epoetin Alfa (N=172)	Placebo (N=22)
Baseline hemoglobin (g/dL)		
Mean±SD	9.9±1.11	9.2±0.98
Median	9.9	9.4
Range	6.3-13.6	6.6-10.9
Day of response		
Mean±SD	52±28.2	75±45.6
Median	47	68
Range	10-188	15-170
Hemoglobin at response (g/dL)		
Mean±SD	12.8±1.18	11.8±0.77
Median	12.7	11.9
Range	10.0-16.0	9.7-12.9
Day of maximum hemoglobin		
Mean±SD	92±43.6	105±54.2
Median	89	88
Range	15-287	22-205
Maximum hemoglobin (g/dL)		
Mean±SD	14.2±1.56	12.2±0.98
Median	14.3	12.0
Range	10.0-17.7	9.7-14.7
Day of last hemoglobin		
Mean±SD	129±49.4	141±54.9
Median	125	132
Range	24-287	66-258
Last hemoglobin (g/dL)		
Mean±SD	12.9±1.87	11.6±1.47
Median	13.1	11.9
Range	7.5-17.6	8.9-14.5

NOTE: Transfusion-related hemoglobin values on study were excluded.

Proportion of Correctors. Overall, there were significantly ($p<0.001$) more correctors (67.6%) in the epoetin alfa group than in the placebo group (15.7%) (Table 22). This effect was maintained when an evaluation of the proportion of correctors by tumor type (solid or hematological) and hemoglobin stratum (≤10.5 g/dL or >10.5 g/dL) was performed; the proportion of correctors was greater in the epoetin alfa group than in the placebo group regardless of tumor type or hemoglobin stratum (Table 23).

Within the epoetin alfa group, the proportion of correctors was slightly greater in subjects with hematological vs. solid tumors, and in subjects in the higher vs. lower hemoglobin stratum.

Among the correctors, the mean study day that they achieved a hemoglobin level of at least 12 g/dL was reached earlier in the epoetin alfa group (52 days) compared with the placebo group (80 days) (Table 24).

Table 22: Proportion of Correctors (Subjects Who Achieved a Hemoglobin ≥12 g/dL Unrelated to Transfusions) (Efficacy Population)

Correction	Epoetin Alfa (N=244)		Placebo (N=115)		p value[a]
Corrector	165	(67.6%)	18	(15.7%)	<0.001
Noncorrector	79	(32.4%)	97	(84.3%)	

[a] Fisher's Exact test.

Table 23: Proportion of Correctors (Subjects Who Achieved a Hemoglobin ≥12 g/dL Unrelated to Transfusions) by Subgroup (Efficacy Population)

Subgroup	Epoetin Alfa (N=244)		Placebo (N=115)	
Tumor Type				
Solid	83/131	(63.4%)	10/61	(16.4%)
Hematological	82/113	(72.6%)	8/54	(14.8%)
Hemoglobin Stratum				
≤10.5 g/dL	127/203	(62.6%)	14/100	(14.0%)
>10.5 g/dL	38/41	(92.7%)	4/15	(26.7%)

Table 24: Summary of Correctors (Subjects Who Achieved a Hemoglobin ≥12 g/dL Unrelated to Transfusions) (Correctors in Efficacy Population)

	Epoetin Alfa (N=165)	Placebo (N=18)
Baseline hemoglobin (g/dL)		
Mean±SD	10.1±1.12	10.2±1.40
Median	10.1	10.4
Range	6.3-14.3	6.6-12.6
First day of hemoglobin ≥12 g/dL		
Mean±SD	52±31.1	80±42.0
Median	47	77
Range	8-188	13-205
First hemoglobin ≥12 g/dL		
Mean±SD	12.9±0.69	12.5±0.56
Median	12.7	12.3
Range	12.1-15.5	12.1-14.0
Day of maximum hemoglobin		
Mean±SD	95±43.1	102±50.4
Median	90	95
Range	15-287	13-205
Maximum hemoglobin (g/dL)		
Mean±SD	14.4±1.34	12.8±0.69
Median	14.4	12.5
Range	12.1-17.7	12.1-14.7
Day of last hemoglobin		
Mean±SD	134±47.2	124±48.6
Median	126	113
Range	24-287	47-205
Last hemoglobin (g/dL)		
Mean±SD	13.0±1.75	12.1±1.13
Median	13.2	12.2
Range	7.5-17.6	9.6-14.5

NOTE: Transfusion-related hemoglobin values on study were excluded.

Final Response. The final response was evaluated for subjects who were on study for at least 56 days. As shown in Table 25, the percentage of subjects who had an increase in hemoglobin level of at least 2 g/dL (rising response) was approximately 3.5 times greater in the epoetin alfa group (51.8%) than in the placebo group (14.3%). One should note that the percentages presented for a rising final response are lower than those presented earlier in this section for proportion of responders (70.5% for epoetin alfa vs. 19.1% for placebo); this difference is due to the fact that the proportion of responders was calculated for subjects who were on study for at least 28 days (N=359) while final response was calculated for subjects who were on study for at least 56 days (N=329). In addition, 'final response' (four categories) is based on the change of hemoglobin from baseline to study termination, excluding interim hemoglobin values, whereas 'response' (two categories) is an

increase of ≥2 g/dL at any time during the study. The percentage of subjects who had an increase in hemoglobin level of less than 2 g/dL (holding response), or a decrease in hemoglobin level with a transfusion (nonresponding) or without a transfusion (declining response) after Day 28, was lower in the epoetin alfa group (29.9%, 11.2%, and 5.8%, respectively) compared with the placebo group (41.0%, 24.8%, and 18.1%, respectively). The difference between the randomized treatment groups in final response was statistically significant ($p<0.001$).

Table 25: Summary of Final Response (Efficacy Population)

Response Category[a]	Epoetin Alfa (N=224)	Placebo (N=105)	p value[b]
			<0.001
1	116 (51.8%)	15 (14.3%)	
2	67 (29.9%)	43 (41.0%)	
3	13 (5.8%)	19 (18.1%)	
4	25 (11.2%	26 (24.8%)	
Unknown	3 (1.3%)	2 (1.9%)	

[a] Final response categories:
1 = Rising response: increase in hemoglobin ≥2.0 g/dL (≥1.24 mmol/L);
2 = Holding response: increase in hemoglobin 0 - <2 g/dL (0-1.24 mmol/L);
3 = Declining response: any fall in hemoglobin and no transfusion after Day 28;
4 = Nonresponding: any fall in hemoglobin and transfused after Day 28.
[b] Wilcoxon rank-sum test.

Predictive Algorithms for Response

Potential predictive algorithms, based on serum erythropoietin levels at two weeks, serum ferritin levels at two weeks, changes in hemoglobin levels to two and four weeks and changes in reticulocyte counts to two and four weeks, were evaluated for their ability to predict the response to epoetin alfa. Responders were defined as subjects achieving a hemoglobin level of ≥2 g/dL above baseline (unrelated to transfusions, ie at least four weeks after a transfusion) at any time during the study. The results are shown in Table 26.

The conditions which were expected to indicate a high probability of response after two weeks of epoetin alfa treatment included: 1) serum erythropoietin levels <100 mU/mL together with an increase in hemoglobin

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2) serum ferritin levels ≥400 μg/L; 3) an increase in hemoglobin of <0.5 g/dL together with an increase in reticulocytes of $<40 \bullet 10^9$/L; and, after four weeks of epoetin alfa treatment, 4) an increase in hemoglobin of <1.0 g/dL together with an increase in reticulocytes of $<40 \bullet 10^9$/L. The response rates in the epoetin alfa treatment group for subjects who met these criteria were 62.1%, 63.8%, 55.0% and 54.8% respectively. These response rates are markedly higher than those found in previous studies for subjects in these categories (Krantz SB. *Blood* (1991) 77: 419-434, Beckman BS, Mason-Garcia M. *The Faseb Journal* (1991) 5: 2958-2964). These findings may be explained in part by slight differences in the definition of responders, but it is also worth noting that the proportions of responders in the epoetin alfa treatment group who met these "negative" conditions were higher than the corresponding proportions of spontaneous responders in the placebo treatment group (Table 26), and were more likely to have had their dose of study drug doubled than the epoetin alfa-treated subjects in the other categories. These results show that it is much more difficult to predict non responders than it is to predict responders and suggest that subjects who would otherwise be predicted to be non responders might respond to a higher dose of epoetin alfa. It is interesting to note that 29 (53%) of the 55 subjects in the epoetin alfa treatment group who had their dose doubled due to non-response after four weeks of treatment eventually did respond at some point later in the study.

Prognostic values of randomized treatment group, change of transferrin receptor value from baseline to two weeks on study, and of neutrophil count at baseline were also investigated in these analyses. Each component of each algorithm was corrected for the other components of the same algorithm.

Treatment with epoetin alfa, increase in hemoglobin level after two or four weeks of treatment, and decrease in ferritin level after two weeks of treatment were each significantly ($p \leq 0.001$) associated with a better final response. Increase in transferrin receptor level after two weeks of treatment approached significance in this simple model ($p=0.075$).

Increase in serum erythropoietin concentration after two weeks of treatment, increase in percent reticulocyte count after two or four weeks (or before the next chemotherapy cycle) of treatment, and baseline absolute neutrophil count were not associated with final response.

These analyses suggest that changes in hemoglobin, ferritin and transferrin receptor levels after two weeks could be of value in allowing an early assessment of the subject for potential response prediction. In addition, changes in erythropoietin levels and reticulocyte counts appear to be less useful for response prediction.

Performance Status

For the efficacy population, the change from baseline to the last value in ECOG performance status by treatment group is summarized in Table 27. A greater percentage of subjects in the epoetin alfa group (20.1%) had a decrease in performance score of one or two points (indicating an improvement in condition), compared with the placebo group (15.6%). Conversely, a lower percentage of subjects in the epoetin alfa group (28.2%) had an increase in performance score of one to four points (indicating a worsening in condition), compared with the placebo group (34.8%).

Overall, the difference between the treatment groups in change from baseline to last value in ECOG performance status was not statistically significant under the stringent statistical analyses performed for the principles of Good Clinical Practices, however the data shows improvement in the physical performance of the erythropoietin treated patients.

Table 27: Change from Baseline to Last Value in ECOG Performance Status, by Treatment Group (Efficacy Population)

	Epoetin Alfa (N=244)	Placebo (N=115)	p value[b]
Change in performance score[a] from baseline to last value			0.239
-2	7 (2.9%)	2 (1.7%)	
-1	42 (17.2%)	16 (13.9%)	
0	126 (51.6%)	56 (48.7%)	
1	41 (16.8%)	29 (25.2%)	
2	14 (5.7%)	7 (6.1%)	
3	12 (4.9%)	4 (3.5%)	
4	2 (0.8%)	0 (0.0%)	
Missing Value	0 (0.0%)	1 (0.9%)	
	(N=244)	(N=114)	
Mean±SD	0.2±1.10	0.3±0.97	
Median	0.0	0.0	
Range	-2.0-4.0	-2.0-3.0	

[a] ECOG Performance score:
0 = able to carry out all normal activity without restriction;
1 = restricted in physically strenuous activity but ambulatory and able to do light work;
2 = ambulatory and capable of all self-care but unable to carry out any work;
3 = capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4 = completely disabled; cannot carry out any self care; totally confined to bed or chair.
[b] Wilcoxon rank-sum test

The change from baseline to the last value in ECOG performance status by response to chemotherapy is summarized in Table 28. Response to chemotherapy is discussed in Response to Chemotherapy.

Table 28: Change in Performance Status, Stratified by Response to Chemotherapy (Efficacy Population)

Response to Chemotherapy[a]	Change from Baseline to Last Value	Epoetin Alfa (N=244)	Placebo (N=115)
Complete response	-2	2 (4.4%)	0 (0.0%)
	-1	12 (26.7%)	0 (0.0%)
	0	26 (57.8%)	9 (90.0%)
	1	5 (11.1%)	1 (10.0%)
Partial response	-2	4 (6.2%)	1 (3.4%)
	-1	20 (30.8%)	8 (27.6%)
	0	32 (49.2%)	14 (48.3%)
	1	7 (10.8%)	6 (20.7%)
	2	1 (1.5%)	0 (0.0%)
	3	1 (1.5%)	0 (0.0%)
No response	-2	1 (1.7%)	0 (0.0%)
	-1	7 (11.9%)	5 (20.0%)
	0	39 (66.1%)	11 (44.0%)
	1	8 (13.6%)	8 (32.0%)
	2	2 (3.4%)	1 (4.0%)
	3	1 (1.7%)	0 (0.0%)
	4	1 (1.7%)	0 (0.0%)
Progressive disease	-2	0 (0.0%)	1 (2.0%)
	-1	3 (4.0%)	3 (6.0%)
	0	29 (38.7%)	22 (44.0%)
	1	21 (28.0%)	14 (28.0%)
	2	11 (14.7%)	6 (12.0%)
	3	10 (13.3%)	4 (8.0%)
	4	1 (1.3%)	0 (0.0%)

Cochran-Mantel Haenszel test stratified by response to chemotherapy: p-value = 0.61.
NOTE: missing response set to unresponsive.

[a] Response to chemotherapy categories:
Complete response = complete absence of detectable tumor;
Partial response = reduction in estimated tumor mass by ≥50%, no new lesions;
No response = reduction of tumor mass <50%, no new lesions;
Progressive disease = increase in estimated tumor mass by ≥25% or appearance of new lesion.

For subjects who showed a complete response to chemotherapy, a greater proportion of subjects in the epoetin alfa group (31.1%) had an improvement in performance score (i.e., decrease in score of at least one point) compared with subjects in the placebo group (0.0%); the proportion of subjects who had a worsening in performance score (i.e., increase in score of at least one point) was similar for the epoetin alfa (11.1%) and placebo (10.0%) groups. For subjects who showed a partial response to chemotherapy, a greater proportion of subjects in the epoetin alfa group (37.0%) had an improvement

in performance score compared with subjects in the placebo group (31.0%); the proportion of subjects who had a worsening in performance score was lower for the epoetin alfa group (13.8%) compared with the placebo group (20.7%).

For subjects who showed no response to chemotherapy, a greater proportion of subjects in the placebo group (20.0%) had an improvement in performance score compared with subjects in the epoetin alfa group (13.6%); the proportion of subjects who had a worsening in performance score was lower for the epoetin alfa group (20.4%) compared with the placebo group (36.0%). For subjects with progressive disease despite chemotherapy, a greater proportion of subjects in the placebo group (8.0%) had an improvement in performance score compared with subjects in the epoetin alfa group (4.0%); the proportion of subjects who had a worsening in performance score was lower for the placebo group (48.0%) compared with the epoetin alfa group (57.3%).

Overall, after correcting for response to chemotherapy, the difference between the treatment groups in change from baseline to last value in ECOG performance status was not statistically significant under the stringent statistical analyses performed for the principles of Good Clinical Practices.

Enhanced Survivability

One of the areas of interest in cancer trials is the impact of the intervention on survival. Previous studies have shown that cancer patients treated with Epoetin alfa and chemotherapy are less likely to be anemic or require transfusions, and therefore are able to tolerate the full dose of chemotherapy and have improved overall quality of life. It is hypothesized that these benefits may also translate into an improvement in survival.

This data is a follow-up of cancer patients in this trial to assess the survival benefits of treatment with Epoetin alfa and non-platinum containing chemotherapy. The survival status was assessed during the post-study period.

Table 28.1

Survival Status by Tumor Type

Diagnose	Status	Epoetin alfa (N= 251) N (%)	Placebo (N= 124) N (%)	Overall (N= 375) N (%)
Breast	Alive	40 (51.3)	13 (36.1)	53 (46.5)
	Dead	35 (44.9)	23 (63.9)	58 (50.9)
	Lost	3 (3.8)	0 (0.0)	3 (2.6)
NHL	Alive	25 (61.0)	12 (57.1)	37 (59.7)
	Dead	16 (39.0)	9 (42.9)	25 (40.3)
Myeloma	Alive	24 (64.9)	12 (48.0)	36 (58.1)
	Dead	11 (29.7)	13 (52.0)	24 (38.7)
	Lost	2 (5.4)	0 (0.0)	2 (3.2)
HL	Alive	18 (94.7)	6 (100.0)	24 (96.0)
	Dead	1 (5.3)	0 (0.0)	1 (4.0)
CLL	Alive	8 (50.0)	4 (80.0)	12 (57.1)
	Dead	6 (37.5)	1 (20.0)	7 (33.3)
	Lost	2 (12.5)	0 (0.0)	2 (9.5)
Gastrointestinal	Alive	6 (35.3)	1 (25.0)	7 (33.3)
	Dead	10 (58.8)	3 (75.0)	13 (61.9)
	Lost	1 (5.9)	0 (0.0)	1 (4.8)
Ovarian	Alive	4 (40.0)	0 (0.0)	4 (23.5)
	Dead	6 (60.0)	7 (100.0)	13 (76.5)
Other	Alive	3 (30.0)	2 (33.3)	5 (31.3)
	Dead	7 (70.0)	4 (66.7)	11 (68.8)
Lung	Alive	1 (10.0)	0 (0.0)	1 (7.7)
	Dead	9 (90.0)	3 (100.0)	12 (92.3)
Pancreas	Alive	1 (20.0)	0 (0.0)	1 (14.3)
	Dead	4 (80.0)	2 (100.0)	6 (85.7)
Prostate	Dead	4 (100.0)	3 (100.0)	7 (100.0)
Sarcoma	Alive	0 (0.0)	2 (40.0)	2 (28.6)
	Dead	1 (50.0)	3 (60.0)	4 (57.1)
	Lost	1 (50.0)	0 (0.0)	1 (14.3)
Diagnose	Status on 15 Nov 1998	Epoetin alfa (N= 251) N (%)	Placebo (N= 124) N (%)	Overall (N= 375) N (%)
Unknown	Alive	1 (50.0)	0 (0.0)	1 (33.3)
	Dead	0 (0.0)	1 (100.0)	1 (33.3)
	Lost	1 (50.0)	0 (0.0)	1 (33.3)
Overall	Alive	131 (52.2)	52 (41.9)	183 (48.8)
	Dead	110 (43.8)	72 (58.1)	182 (48.5)
	Lost	10 (4.0)	0 (0.0)	10 (2.7)

Quality f Life

The quality-of-life intent-to-treat population included subjects who were randomized, received drug, and had a quality-of-life assessment completed at baseline. Change in the quality-of-life measures within and between treatment groups was assessed for the quality-of-life intent-to-treat population.

By Week 16, the treatment effect of epoetin alfa on health-related quality of life was very apparent. Focusing the analysis on the change scores calculated between baseline and last assessment for the seven primary quality-of-life scales, the Total FACT-G, the FACT-An Fatigue, and the three CLAS scales showed strong advantages for subjects randomized to epoetin alfa compared with placebo (p-values, adjusted for multiple comparisons: 0.0036, 0.0036, 0.0007, 0.0018, and 0.0036, respectively). The SF-36 physical and mental component scales did not indicate any detrimental effects due to the administration of epoetin alfa on overall physical and mental quality of life with the mean change score for both scales favoring epoetin alfa but failing to reach statistical significance (p-values, adjusted for multiple comparisons: 0.0512 and 0.0952, respectively). After accounting for subjects who died on study, the results obtained at last assessment were confirmed (with the exception that the between-group difference for the Total FACT-G still favored epoetin alfa but was no longer statistically significant).

Multivariate analyses confirmed the univariate analyses, indicating an advantage to epoetin alfa for the Total FACT-G, the FACT-An Fatigue, and the three CLAS scales (p-values, adjusted for multiple comparisons: 0.0444, 0.0306, 0.0182, 0.0444, 0.0444, respectively). This advantage appears to have carried over into the low hemoglobin (≤10.5 g/dL) and the hematological tumor subgroups. An additional analysis modeling treatment effects in an hypothetical population containing only subjects exhibiting no disease progression indicated that mean quality-of-life change scores could be expected to show a strong advantage for epoetin alfa in cancer-specific quality-of-life domains.

A strong, positive association was found between the seven primary quality-of-life scale scores and hemoglobin levels, as well as strong associations between changes in hemoglobin levels and changes in quality-of-life scores. The treatment-specific effect upon hemoglobin, conjoined with the positive association of hemoglobin and subject quality of life, helps to explain the treatment-specific effect on subject quality of life found in this study.

Overall, these data support a strong treatment effect for epoetin alfa on cancer-specific quality-of-life domains among non-myeloid cancer patients receiving non-platinum containing chemotherapy. Additionally, there appears to be no decrement in overall physical and mental quality of life (as measured by the SF-36 summary scales) relative to placebo for subjects randomized to epoetin alfa. Therefore, this study demonstrates a strong treatment effect for epoetin alfa on cancer-specific quality-of-life domains, consistent with a mechanism of action mediated by an increase in hemoglobin levels.

EFFICACY CONCLUSIONS

This study has demonstrated the effectiveness of epoetin alfa in the treatment of anemia in subjects receiving non-platinum containing chemotherapy for non-myeloid malignancies. In addition, this study also shows evidence that suggests that epoetin alfa is effective in the prevention of anemia in this subject population.

Evaluation of the primary efficacy variable showed that the proportion of subjects transfused after Day 28 was significantly lower in the epoetin alfa-treated group than in the placebo-treated group ($p=0.0057$ for the intent-to-treat population and $p=0.0168$ for the efficacy population). In addition, regardless of tumor type (solid or hematological) or hemoglobin stratum (≤ 10.5 g/dL or >10.5 g/dL), the proportion of subjects transfused after Day 28 was lower in the epoetin alfa group than in the placebo group. The logistic regression results with treatment group, tumor type, and hemoglobin stratum as covariates showed that the effect of tumor type on the proportion of subjects transfused after Day 28 was not statistically significant for either the intent-to-treat ($p=0.43$) or efficacy ($p=0.19$) populations. The effect of

hemoglobin stratum as a covariate was statistically significant for both the intent-to-treat (p=0.0017) and efficacy (p=0.0022) populations.

Additional transfusion-related results supported those of the primary efficacy variable. The proportion of subjects transfused or with a hemoglobin level below 8 g/dL after Day 28 was significantly lower in the epoetin alfa group than in the placebo group (p=0.0002). Of the subjects who were transfusion dependent at baseline, a greater percentage of epoetin alfa-treated subjects (60.6%) became transfusion independent after Day 28 (i.e., not transfused or no hemoglobin below 8 g/dL after Day 28) compared with placebo-treated subjects (28.2%). Conversely, of the subjects who were transfusion independent at baseline, a lower percentage of epoetin alfa-treated subjects (19.1%) became transfusion dependent after Day 28 (i.e., transfused or with a hemoglobin below 8 g/dL after Day 28) compared with placebo-treated subjects (31.6%). For all subjects who were transfused after Day 28, the median cumulative transfusion rate was lower in the epoetin alfa group (3.8 units per three months on study) than in the placebo group (4.7 units per three months on study). For subjects who were transfusion independent at baseline who became transfusion dependent after Day 28, the median cumulative transfusion rate was also lower in the epoetin alfa group (3.8 units per three months on study) than in the placebo group (5.2 units per three months on study).

The time to first transfusion after Day 28 was significantly (p=0.0001) longer for subjects in the epoetin alfa group than for subjects in the placebo group.

Evidence of the effect of epoetin alfa on hematopoietic variables was shown by significantly greater increases from baseline to last value in hemoglobin level (p<0.001), hematocrit (p<0.001), and reticulocyte count (p=0.037) compared with placebo, despite the fact that placebo subjects received more transfusions during the study. There were significantly (p<0.001) more responders (subjects whose hemoglobin level increased by at least 2 g/dL during the study and who were on study for at least 28 days) and correctors (subjects who achieved a hemoglobin level of at least 12 g/dL during the study and who were on study for at least 28 days) in the epoetin alfa group

than in the placebo group. The mean study day that responders achieved a hemoglobin level of at least 2 g/dL above baseline and correctors achieved a hemoglobin level of at least 12 g/dL was reached earlier in the epoetin alfa group (52 days, for either responders or correctors) than in the placebo group (75 and 80 days, respectively). The percentage of subjects who had a rising final response (subjects whose hemoglobin level increased by at least 2 g/dL and who were on study for at least 56 days) was approximately 3.5 times greater in the epoetin alfa group (51.8%) than in the placebo group (14.3%). The difference between the randomized treatment groups in final response was statistically significant ($p<0.001$).

Evaluation of hematopoietic variables by hemoglobin stratum (≤10.5 g/dL or >10.5 g/dL) provided evidence of epoetin alfa's effectiveness in preventing the worsening of anemia. Mean increases from baseline to last value in hemoglobin and hematocrit levels were much greater in the epoetin alfa group compared with the placebo group regardless of hemoglobin stratum. Within the epoetin alfa group, the mean increases in hemoglobin and hematocrit levels were similar for the low and high hemoglobin stratum. For subjects stratified to the >10.5 g/dL hemoglobin level, the mean hemoglobin levels were maintained or increased between Weeks 2 and 16 in the epoetin alfa group compared with the placebo group, indicating that early treatment with epoetin alfa can prevent anemia requiring transfusion. The proportion of responders and correctors was also greater in the epoetin alfa group than in the placebo group regardless of tumor type or hemoglobin stratum. Changes in hemoglobin, ferritin and transferrin receptor levels may be useful to assess response prediction as early as two weeks after start of treatment with epoetin alfa.

Overall, there were no significant differences between treatment groups in change from baseline to last value in ECOG performance status, either unstratified or stratified by response to chemotherapy.

Quality-of-life data support a strong treatment effect for epoetin alfa on cancer-specific quality-of-life domains in this subject population, consistent with a mechanism of action mediated by an increase in hemoglobin levels.

The SF-36 physical and mental component scales favored epoetin alfa but failed to reach statistical significance.

Safety Results

DATA SET ANALYZED

Results are provided in this section for the safety population which included all subjects who received at least one dose of study drug and for whom safety information was available. Safety data for all 375 subjects enrolled in the study are summarized in this report, including 251 subjects who received epoetin alfa and 124 subjects who received placebo. In this study, the safety population was the same as the intent-to-treat population.

DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Since the safety and intent-to-treat populations were the same for this study, refer to Demographic and Baseline Characteristics, in which demographic and baseline characteristics were discussed for the intent-to-treat population.

EXTENT OF EXPOSURE

A summary of the mean weekly dose of study drug is presented in Table 29 and Figure 7 for the intent-to-treat population. The mean weekly dose of study drug was similar for the two treatment groups for the first four weeks of treatment. For all weeks between Weeks 5 and 34, the mean weekly dose of study drug was lower in the epoetin alfa group than in the placebo group. The summary of mean weekly dose of study drug was similar for the efficacy population to that described for the intent-to-treat population.

Table 29: Mean Weekly Dose of Study Drug (IU/kg/week) (Intent-to-Treat Population)

	Epoetin Alfa (N=251)			Placebo (N=124)		
Week[a]	N	Mean	SD	N	Mean	SD
1	251	485	70.8	123	494	69.4
2	251	441	57.1	122	451	54.9
3	249	456	65.3	121	458	46.5
4	247	461	92.3	118	469	105.9
5	241	499	167.1	115	586	221.3
6	240	498	188.1	113	627	229.0
7	232	500	206.3	112	643	250.2
8	226	492	220.2	108	636	244.2
9	217	508	244.6	98	656	249.3
10	207	485	240.2	95	644	275.0
11	194	464	269.2	90	656	263.3
12	183	456	264.4	81	657	274.1
13	174	453	277.4	70	633	271.0
14	153	429	284.2	58	607	271.6
15	146	427	294.5	53	605	286.3
16	137	412	297.8	47	599	283.6
17	112	419	303.9	41	598	276.4
18	101	412	300.2	36	607	241.9
19	89	373	297.4	34	614	246.1
20	86	360	288.5	30	615	259.4
21	68	349	297.7	26	611	248.6
22	60	330	283.5	22	566	274.4
23	57	309	284.5	19	581	252.2
24	52	316	300.8	18	543	236.0
25	41	307	288.2	12	585	221.3
26	34	352	279.0	11	582	234.8
27	30	317	252.9	11	499	280.2
28	22	387	237.3	8	495	262.8
29	11	342	191.5	5	492	280.2
30	8	389	193.2	2	691	342.0
31	8	394	175.9	2	691	343.7
32	7	386	201.5	2	848	566.0
33	7	423	226.2	2	693	347.2
34	7	337	226.8	1	447	-
35	1	526	-	1	447	-
36	1	395	-	1	447	-
37	1	526	-	1	447	-
38	1	395	-	-	-	-
39	1	526	-	-	-	-
40	1	395	-	-	-	-
41	1	526	-	-	-	-

[a] Week calculated from the day of study drug administration. Incomplete last weeks omitted.

The cumulative percentage of subjects whose weekly dose of study drug was doubled was consistently higher in the placebo group than in the epoetin alfa group starting at Week 4 and continuing throughout the study; this indicates that a greater percentage of placebo-treated subjects than epoetin alfa-treated

subjects did not reach the hematologic values to continue the same regimen. In the intent-to-treat population, 22% (55) of 251 subjects randomized to epoetin alfa had their dose doubled; of these, 22 subjects were stratified to solid tumor types and 33 subjects to hematological tumor types. The mean cumulative percentage of subjects whose weekly dose of study drug was withheld was consistently higher in the epoetin alfa group than in the placebo group starting at Week 2 and continuing throughout the study (with the exception of Week 4); this indicates that a greater percentage of epoetin alfa-treated subjects than placebo-treated subjects had a hemoglobin level that exceeded 15 g/dL at some time during the study which required study drug to be withheld until the hemoglobin level decreased below 12 g/dL. The mean cumulative percentage of subjects whose weekly dose of study drug was reduced was consistently higher in the epoetin alfa group than in the placebo group starting at Week 2 and continuing throughout the study; this indicates that a greater percentage of epoetin alfa-treated subjects than placebo-treated subjects had a hemoglobin level that rose at a rate ≥2 g/dL per month or per cycle requiring the dose of study drug to be reduced by approximately 25% to maintain the rate of rise of hemoglobin to <2 g/dL per month or per cycle. The summary of weekly cumulative number and percentage of subjects whose dose of study drug was doubled, withheld, or reduced was similar for the efficacy population to that described for the intent-to-treat population.

EXAMPLE 2

RANDOMIZED STUDY TO COMPARE THE EFFECT OF EARLY INTERVENTION AND/OR TREATMENT WITH EPOETIN ALFA VS CONVENTIONAL CARE ON ANEMIA IN OVARIAN CANCER SUBJECTS RECEIVING PLATINUM-BASED CHEMOTHERAPY.

SYNOPSIS

OBJECTIVES:

To evaluate the effect of early intervention with Epoetin alfa on anemia and fatigue in subjects with ovarian cancer who are undergoing platinum-based **chemotherapy.** The endpoints will be:

- Complete Haematological response to Epoetin alfa, defined as an increase in hemaglobin of at least 2 g/dL from baseline.
- Change in Quality of Life scores for Anemia and Fatigue from baseline as measured by the FACT-An scale and the Cancer Linear Analogue Scale.
- To assess the safety of Epoetin alfa when used in the prevention of anemia during platinum-based chemotherapy

OVERVIEW OF STUDY DESIGN:

This is a Phase IV randomised, open label, multicentre trial in 201 subjects. They will be randomly assigned in a 2:1 ratio to one of the two treatment arms, Epoetin alfa, 150 IU/kg (10,000 IU) 3x/week, or conventional care. Subjects will receive study medication until 4 weeks after the last dose of chemotherapy.

STUDY POPULATION:

201 subjects with confirmed diagnosis of ovarian malignancy (any stage), receiving platinum-containing chemotherapy for at least 8 weeks (two or more chemotherapy cycles).

Subjects will be at least mildly anaemic having a hemaglobin level at entry of ?12.0g/dL (7.44 mmol/l). The assumption is that worsening of anemia is a likely consequence of further chemotherapy and or the underlying disease.

DOSAGE AND ADMINISTRATION:

Subjects randomised to Epoetin alfa will receive either 150 IU/kg or 10,000 IU Epoetin alfa, SC, 3x/week from a phosphate buffered pre-filled syringe formulation. Subjects randomised to the control group will receive identical treatment as they would were they not enrolled in a clinical trial, according to each individual centre's normal practices. Monthly reticulocyte count and/or hemaglobin level will determine whether the same dose or an adjusted dose will be used for the remainder of the treatment.

EFFICACY EVALUATIONS/CRITERIA:

Main efficacy parameter:

- Haematological response to Epoetin alfa, defined as an increase in hemaglobin of at least 2 g/dL from baseline, (complete response, and see secondary parameters below).

Secondary efficacy parameters:

- Change in Quality of Life scores for Anemia and Fatigue from baseline as measured by Adapted Linear Analogue Scale and FACT-An.
- Number of blood transfusions.
- Tumour Response to Chemotherapy.
- Partial haematological response, defined as an increase in hemaglobin of 1-1.99 g/dL from baseline
- Holding response, defined as an increase in hemaglobin of up to 0.99 g/dL from baseline combined with an increase in reticulocytes of > 40,000/µl
- Treatment failure is defined as no change, or a fall in hemaglobin level from baseline associated with an increase in reticulocytes <40,000/µl.

SAFETY EVALUATIONS:
Assessment of laboratory tests, vital signs and incidence and severity of adverse events associated with study drug administration.

TIME AND EVENTS SCHEDULE:
The time and events schedule for this study is shown on the following page

TIME AND EVENTS SCHEDULE - EPO-INT-45

Visit	Pre-Treatment[A] 1	On-Study Visits 2	3	4	5	6 (Study Completion or Early Termination) [E]
Week of Study * (completed)	1	4-6*	8-9*	12	16-18*	22-28 (maximum)**
Informed Consent	X					
Medical History (incl. Previous chemotherapy)	X					
Physical Examination	X					X
Current Therapy	X					
Ovarian Malignancy Staging	X					X
Laboratory Tests: **Haematology** - hemaglobin - haematocrit - RBC - WBC - platelet count - reticulocyte count	X	X[B]	X[B]	X[B]	X[B]	X
Iron Parameters - serum iron - ferritin - transferrin - TIBC	X	X[B]	X[B]	X[B]	X[B]	X
Vital Signs	X	X[B]	X[B]	X[B]	X[B]	X
ECOG Performance Score	X	X[B]	X[B]	X[B]	X[B]	X
Randomisation	X					
QoL Assessment - CLAS	X	X[B]	X[B]	X		X
- FACT-An	X		X[B]			X
Transfusion Data	X	X	X	X	X	X
Chemotherapy Data[C]	X	X	X	X	X	X
Tumour Response						X
Epoetin alfa dosing		X	X	X	X	X
Adverse Events[D]		X	X	X	X	X

* Variable according to either 3 or 4 weekly chemotherapy cycles. ** 4 weeks after end of chemotherapy

A. All procedures to be performed within 7 days of first study medication dose.

B. To be performed before start of next chemotherapy cycle.

C. All assessments must be done prior to administration of chemotherapy regimen.

D. Including concomitant therapy.

E. All procedures to be performed within 5 days after last dose of study medication.

OVERVIEW OF STUDY DESIGN

This is a Phase IV randomised multicentre trial in 201 adult ovarian cancer subjects aged older than 18 years who are receiving platinum containing chemotherapy. Subjects will be randomised in a 2:1 ratio to Epoetin alfa or no Epoetin alfa (control group, normal care). The subjects randomised to Epoetin alfa will receive 150 IU/kg of Epoetin alfa (10,000 IU or 5,000 IU if under 45 kg) three times a week until on study chemotherapy cycles are complete. All subjects will receive best supportive care. Eligibility of all subjects will be determined by the inclusion and exclusion criteria listed herein.

Subjects should not have been transfused during the cycle of therapy before being enrolled in this study (last 14 days). Transfusions may be administered as necessary during the study. Based on clinical judgement, every effort should be made not to transfuse subjects who have an Hb > 9 g/dL.

The study population will comprise subjects who are at least mildly anaemic, Hb level ≤12.0 g/dL (7.44mmol/l) and assumes that worsening of anemia is a likely consequence of further chemotherapy and or the underlying disease. Study drug administration will start as soon as entry criteria have been satisfied, which should coincide with the start of the next chemotherapy cycle.

STUDY POPULATION

General Considerations

201 ovarian cancer subjects receiving platinum-containing chemotherapy, who meet the following criteria on pre-study examination, will be enrolled into the study. The specific inclusion and exclusion criteria for enrolling subjects in this study are described in the following sections. Exceptions to these inclusion/exclusion criteria should occur infrequently and should be discussed in advance with the Janssen-Cilag European Medical Affairs Central/Local Trial Coordinator. If an exception is agreed upon and a subject is allowed to participate, the medical monitor will send confirmation to the site acknowledging the exception. This confirmation form or letter is to be kept with the case report forms (CRFs) both at the site and at the sponsor.

Inclusion Criteria

Subjects must satisfy the following criteria to be eligible for the study:

1. Confirmed diagnosis of ovarian cancer, for which platinum based chemotherapy is underway or imminent.

2. Predicted to receive further chemotherapy for at least 8 weeks.
3. At least mild anemia at study entry, defined as a hemaglobin level ≤12.0 g/dL (7.44mmol/l).
4. An ECOG Performance Score of 0, 1, 2, or 3.
5. A life expectancy of 6 months or longer, based on the investigator's clinical judgement.
6. Aged at least 18 years.
7. Female subjects (see exclusion criteria).
8. Subjects must have given their written informed consent, the nature of the study having been fully explained and a written information sheet having been provided.

Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from participating in the study:

1. Clinically significant disease/dysfunction of the pulmonary, cardio-vascular, endocrine, neurological, gastrointestinal, or genitourinary systems not attributable to underlying malignancy or chemotherapy.
2. Uncontrolled hypertension defined as a diastolic blood pressure greater than 95 mm Hg.
3. A history of seizures.
4. Evidence of untreated iron, folate or Vitamin B_{12} deficiency.
5. Blood transfusion within 14 days prior to study entry.
6. Anemia due to factors other than cancer/radiotherapy/chemotherapy (e.g. haemolysis or gastrointestinal bleeding).
7. Acute major illness within 7 days of study entry, or major infection within one month of study entry.
8. Surgery within 7 days prior to study entry.
9. Pregnant or lactating females or females of childbearing potential not currently practising a documented adequate method of contraception. (i.e, hormonal contraceptives, intrauterine device or barrier and spermicide). If a female subject is practising an

acceptable method of birth control, she must continue with the same method during the entire study.

10. Participation in any other investigational drug trial or therapy, relating to anemia, within 30 days of randomisation. Or current inclusion in any other research project involving unlicensed or experimental medications which would interfere with this study (experimental regimes of licensed medications are permitted).

11. Known hypersensitivity to Epoetin alfa or one of its components.

RANDOMIZATION AND BLINDING

Overview

Randomisation will be used to avoid bias in: the assignment of subjects to treatment; in the evaluations; to increase the likelihood that known and unknown subject attributes (e.g., demographics and baseline characteristics) are evenly balanced across treatment arms; to enhance the validity of statistical comparisons.

Procedures

Subjects will be randomly allocated in a 2:1 ratio to receive initially either Epoetin alfa 150 IU/kg (10,000 IU) 3x/week or conventional care. A prospective randomisation procedure will be employed.

Sets of sequential subject numbers will be assigned to investigators. As subjects qualify for study entry, they will be assigned the next available subject number. Sealed code envelopes will be made available to the investigator. These envelopes are to be opened after the eligibility of the subject is confirmed and will contain the treatment arm for the subject, either Epoetin alfa or conventional care.

DOSAGE AND ADMINISTRATION

Clinical experience has indicated that Epoetin alfa in a dose of 150 IU/kg SC 3x/wk can correct anemia in cancer subjects receiving platinum chemotherapy. A fixed dose of 10,000 IU corresponds to 150 IU/kg in a subject having a body weight of 70 kg.

Initial Dosage

Study medication will be provided in pre-filled, single-use 1mL syringes, containing 10,000 IU Epoetin alfa and will be administered by subcutaneous injection three times a week on a basis appropriate to the subject's situation.

Each dose should be separated by at least two days, i.e. dose on Monday, Wednesday, and Friday.

Subjects will receive as a starting dose, 150 IU/kg (10,000 IU) of Epoetin alfa three times a week or no Epoetin alfa.

DOSAGE VARIATIONS

For Subjects with a body weight < 45 kg, the following adjustments will be made:

- Subjects < 45 kg: Subjects will be given a fixed dose of 5,000 IU. S.C. t.i.w. For this purpose single use pre-filled syringes containing 4000 IU and 1000 IU Epoetin alfa will be provided. Alternatively half a 10,000 IU pre-filled syringe may be administered.

Dosage Adjustments

The initial dose will be maintained through the first on-study chemotherapy cycle (4 weeks) for 4 weekly cycles and through 2 cycles (6 weeks) for 3 weekly cycles. If at the end of Week 4/6* the reticulocyte count has not increased by > 40,000/μL or the Hb has not increased by > 1 g/dL above baseline, the dose of Epoetin alfa is to be increased to 300 IU/kg (20,000 IU) S.C. t.i.w.starting at the week 5/7* dose. For Subjects with a body weight < 45 kg, the dose of Epoetin alfa should be increased to 150IU/kg (10,000 IU). S.C. t.i.w.

(* 4/3 weekly cycles respectively)

Subjects should continue on Epoetin alfa until 4 weeks after the end of their last chemotherapy cycle.

If at any time the hemaglobin exceeds 14 g/dL (8.69 mmol/L), the study medication must be withheld until the hemaglobin has fallen below 12 g/dL (7.44 mmol/L), and will then be restarted at a dose 25-50% lower than the dose previously administered.

If the hemaglobin is rising by ≥ 2 g/dL (1.24 mmol/L) per month, the dose of the study medication will be reduced by between 25-50% (depending on the rate of increase) to maintain the rate of increase of hemaglobin to < 2 g/dL per month.

In both the above situations the dosage reduction may be achieved by omiting on of the doses during the week (i.e. reduce to 10,000 IU twice a week).

Do not adjust the Epoetin alfa dose if the increase in hemaglobin is due to a transfusion.

Subjects will be instructed by the investigator or the responsible study nurse on the correct administration technique and schedule for the study medication. The subject has to demonstrate his/her competence to administer self-injections, if this is planned. The Local sponsor will provide instructional material in the subjects' language on the use of pre-filled syringes.

The study medication is to be administered by subcutaneous injection. Each syringe of study medication should be used only once.

CONCOMITANT THERAPY

Note: The use of licensed white cell growth factors is allowed during the study.

Iron supplementation should be given to maintain appropriate iron availability and iron stores so that erythropoiesis is not restricted. A daily dose of 200 mg of elemental iron as oral iron supplementation is recommended. Transferrin saturation > 20% will be considered as indication of adequate iron stores.

Red Cell Transfusions may be administered when clinical judgement deems necessary during the study, but every effort will be made not to transfuse subjects until their hemaglobin is below 9 g/dL (5.58 mmol/L).

Concomitant therapy administered for the treatment of an adverse event (AE) is to be recorded together with the adverse event in the appropriate section of the case report form.

If chemotherapy is discontinued, the subject may continue on Epoetin alfa therapy for up to a total of 4 weeks after the last dose of chemotherapy. At the time chemotherapy is discontinued, the following evaluations must be completed.

- Clinical laboratory tests: Hemaglobin.
- Reason for chemotherapy discontinuation.

In case of a serious adverse event (SAE), all concomitant therapy administered at the time of onset of the SAE must be reported in the case report form.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

STUDY PROCEDURES

Overview

The Time and Events Schedule included in the synopsis summarizes the frequency and timing of the safety and efficacy measurements.

The study is divided into phases with associated evaluations and procedures, which must be performed at the specified time points, as described in the following Sections. A flow chart of the study is provided in the Time and Events Schedule (Synopsis).

Subjects will be evaluated for entry criteria during a screening period of 7 days prior to study treatment start. When found eligible for the trial, they will be given a randomised subject number on the day of the first administration of study medication.

Screening Period

The following procedures will have been completed for each subject within the 7 days prior to administration of the study medication.

- Informed consent. *N.B. Informed consent must be obtained before any procedures are carried out which do not form a part of the subject's normal care or are specifically carried out in order to establish eligibility.*
- Medical history, including chemotherapy (number of cycles, drugs and dosage) for the past three months, and Hb level at the beginning of the current cycle of chemotherapy.
- Vital signs and any symptoms of malignant disease.
- History and staging of malignancy[1].
- Information on previous therapy, including immunotherapy and surgery for the past 4 weeks.

[1] Where ever possible, the TNM or FIGO system for staging of tumours should be used. The investigator may however, use an appropriate and internationally acceptable staging system of his own choice.

- Clinical laboratory tests (after subjects' recovery from previous chemotherapy treatment):

- <u>Haematology</u>:

- hemaglobin[2] - ***For the purpose of this study, baseline screening measurements for haematology to establish eligibility may be obtained from the clinical records of the prospective subjects, provided they form part of the normal clinical management of the patient***

  * Haematocrit
  * Total erythrocyte (RBC) count
  * Total leukocyte (WBC) count.
  * Platelet count
  * Reticulocyte count (μL^{-1})

- <u>Iron status</u>: Any or all of the following should be recorded according to local practice in order to assess the patient's iron status.

  * Serum iron
  * Ferritin
  * Tranferrin
  * TIBC

- ECOG performance score, as determined by investigator.

Randomisation

If the subject is qualified to participate in the study, he/she will be given the next available subject number, which allocates the subject to one of the two treatment arms according to the randomisation schedule previously provided.

The subject should complete the Quality of Life (QoL) questionnaires: FACT An and Cancer Linear Analogue Scale.

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[2]This Hb level measured within seven days of study entry is defined as the baseline Hb for evaluating response to study medication

Study drug administration should be started as soon as entry criteria are satisfied.

Treatment

During treatment phase, subjects are required to visit the investigator's office or clinic at the end of each chemotherapy cycle, i.e. just before starting the next chemotherapy cycle. . During treatment with epoetin alfa (Eprex/Erypo) a gradual increase of hemaglobin of up to 2g/dL/month is recommended. In order to ensure this, it is recommended that hemaglobin is monitored regularly (up to once/week) until the increase in hemaglobin is stable. Thereafter hemaglobin should be monitored periodically (at least monthly). This should be achieved in concord with the treating clinician's judgement, the patients treatment plan and associated clinic attendances. Hemaglobin levels will be recorded in the CRF at the end of selected chemotherapy cycles.

During the study visits (coinciding with the end of a chemotherapy cycle), i.e. just before starting the next chemotherapy cycle, the following data and information will be collected and registered in the individual Case Report Form:

- Details of each Epoetin alfa administration: dates and doses.
- Haematology (Hb, Hct, Retic).
- Details of changes in chemotherapy administered (including type of drugs, dosages and schedule of administration).
- Transfusion information, including Hb level prior to transfusion, volume and type of product transfused (after each chemotherapy cycle).
- Occurrence of adverse event (at each visit).
- Sample collection for iron parameters at the end of each chemotherapy cycle.
- Evaluation of vital signs.
- ECOG performance score.
- **Quality of Life questionnaire: Cancer Linear Analogue Scale after 4 or 6* and 8 or 9* and 12 weeks of epoetin alfa treatment. FACT An, after 8 or 9* weeks. (*3weekly cycles)**

STUDY TERMINATION

A study termination visit will be scheduled within 5 days of last dose of study medication or upon premature withdrawal from the study. Study medication

will be continued for 4 weeks after the end of chemotherapy. The following procedures will be performed:

- Physical examination including vital signs measurements, and any current clinical signs and symptoms of malignant disease.
- Tumour response to radiotherapy and/or chemotherapy.
- Clinical laboratory tests
- Transfusion information, including Hb level prior to transfusion, volume and type of product transfused.
- Possible occurrence of adverse events.
- Details of chemotherapy.
- ECOG performance score, as determined by the investigator.
- Quality of Life questionnaires: FACT An and Cancer Linear Analogue Scale, as completed by subject.

DISCONTINUATION OF CHEMOTHERAPY

If chemotherapy is discontinued, the subject may continue on Epoetin alfa therapy until 4 weeks after the end of chemotherapy. At the time chemotherapy is discontinued, the following evaluations must be completed.

- Clinical laboratory tests: Hemaglobin, routine haematology.
- Tumour response to chemotherapy. Longer term (up to 6 months) follow up may be implemented, but will not require further study visits.
- Reason for chemotherapy discontinuation.

STUDY EVALUATIONS

Primary parameter

As a primary efficacy parameter, the change in hemaglobin from baseline to the end of the study will be analysed for all patients based on intention to treat.

EFFICACY CRITERIA

A Complete response will be defined as those subjects demonstrating an Hb increase of ≥2g/dL above baseline, without having undergone blood transfusions within the proceeding four (4) weeks. Subjects who achieve an increase in hemaglobin ≥2g/dL during the study period, but who have required dosage reduction due to hemaglobin >14.0 g/dL, will still be regarded as complete responders even though the hemaglobin rise as measured at the final visit may not be ≥2g/dL. In essence the aim of the treatment is to establish a near normal hemaglobin level in the range 12-14 g/dL, therefore if a patient achieves a hemaglobin level of 14.0 g/dL, they are regarded as a treatment success.

A partial haematological response, will be defined as an increase in hemaglobin of 1-1.99 g/dL from baseline, whilst a holding response, will be defined as an increase in hemaglobin of up to 0.99 g/dL from baseline baseline combined with an increase in reticulocytes of > 40,000/μl.

Treatment failures are non-responders, defined as either no change or a fall in hemaglobin level, from baseline accompanied by an increase in reticulocytes < 40,000/μl. Non-responders will also include those with a hemaglobin increase that have received blood transfusion within the preceding four weeks.

Secondary parameters

Results will be also analysed in order to assess the change in QoL that results from early intervention and/or treatment with Epoetin alfa in ovarian cancer patients undergoing platinum-containing chemotherapy.

Quality of life and performance status will be assessed at pre-treatment, after 4 or 6 weeks (CLAS only) after 12 weeks and at the completion of the trial.

The quality of life battery, composed of the FACT-An and the Cancer Linear Analogue Scale, is self-administered by the subject and addresses issues of functioning, well-being and specific fatigue experiences. The questionnaires should always be completed in the same order, i.e., starting with the FACT-An, then the Cancer Linear Analogue Scale.

Safety Evaluations

The following safety evaluations will be performed during the study to measure the safety and tolerability of Epoetin alfa

Adverse Events (AEs): AEs will be reported by the subject (or where appropriate by the subject's legally authorized representative) for the duration of the study. AEs will be followed by the investigator to satisfactory resolution, including those persisting beyond the end of the study.

Clinical laboratory tests as follows:

Hematology Panel

- - hemaglobin
- - haematocrit
- - total erythrocyte (RBC) count
- - total leukocyte (WBC) count, including differential (cell counter)
- - platelet count
- - reticulocyte count (μL^{-1})

Vital Signs

Any abnormalities persisting at the end of the study will be followed until resolution, or until reaching a clinically stable endpoint.

SUBJECT COMPLETION

Completion

A subject will be classified as having completed the study if he/she has completed study medication as described herein and has had all evaluations completed at appropriate visits including Study Termination visit. Subjects must complete at least 8 weeks of chemotherapy while taking study medication. Up to 6 chemotherapy cycles (18-24 weeks) are allowed during study participation.

Withdrawal

Subject participation may be terminated prior to completing the study for any of the following reasons:

- Adverse Event
- Subject choice
- Lost to follow-up
- Other

Subjects who withdraw should have the procedure performed as prescribed for the Study Termination visit.

Additionally, the investigator is to retrieve all remaining study drug containers, whether empty or containing drug.

When a subject withdraws prior to completing the study, the reason for withdrawal is to be documented on the CRFs and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced.

STATISTICAL METHODS

The trial design is that of a multi-centre (multinational) randomised, open label, parallel group study. In statistical terms, the model is a two-factor design with treatment and centre as grouping variables.

Efficacy Evaluations

PLANNED ANALYSES

All efficacy and safety parameters will be presented descriptively. Tables of descriptive statistical parameters (number of non-missing values, mean, standard deviation, median, range) and/or frequency tables (number of non-missing values, percentage) will be constructed for each time point and treatment group.

EFFICACY EVALUATIONS

Primary parameter

The main endpoint will be change of Hb from baseline to end of treatment in all patients (intention-to treat). The primary analysis of efficacy of the trial will involve comparison of hemaglobin levels (recorded within 5 days after the last dose of study medication or early termination) across the treatment groups.

Analysis of covariance (ANCOVA), including Hemaglobin's levels at screening as a covariant, will be used to make these comparisons. Terms in the model included: treatment group, centre and treatment by centre interaction.

The analysis of the primary endpoint will be repeated for all intention-to-treat patients, excluding those with major protocol violations. This analysis will be carried out in a manner analogous to the primary analysis.

Secondary ndpoint

Analysis of the secondary endpoints of the trial will employ much of the same techniques as that of the primary analysis. ANCOVA will be used to assess differences between the treatment groups with respect to Quality of Life (AUC).

Secondary endpoints include: Change in QoL between 2 groups; Association between change in Hb and QoL; Partial and holding hemaglobin responses; Final response outcome categories; Cumulative transfusion rate excluding first month relative to the follow-up period; ECOG performance score; Adverse events; Tumour response and follow up information.

The number of responders and non-responders will be summarised and between group comparisons will be carried out using Pearson's X^2-test.

Cumulative transfusion value will be also summarised. Differences between treatment groups will be evaluated by Wilcoxon-Mann-Whitney (WMW) test. This is also the approach that will be used in comparing tumour response and ECOG Performance Scores between treatment groups at each visit. Descriptive statistics will be employed to examine long term follow-up data, which will be reported outside of the main study report.

Safety Evaluations

All individual values will be listed. Vital sign parameters will be assessed by means of descriptive statistical analysis. Laboratory values will be compared to their reference ranges. The product specific WHO-ARD (World Health Organisation Adverse Reaction Dictionary) will be used for the coding of all adverse events reported. In addition, adverse events will be tabulated according to severity and will be categorised by event, body system and preferred term.

No specific hypothesis will be tested with regard to the number of patients that experienced an adverse event

SAMPLE SIZE DETERMINATION

A total of 201 patients is required in order the trial to be completed under the following assumptions: an overall a (probability of Type I error) of 0.025; a (probability of Type II error) of 0.10 or power of 90%; one primary endpoint: Hemaglobin; a difference of 2.0 g/dL between the non-treatment and Epoetin alfa treatment group; a standard deviation of 3.5 g/dL for Hemaglobin; one-

sided test of statistical significance; a random assignment to one of the two treatment arms (EPREX or conventional care) in a 2:1 ratio; a drop-out rate of 40%.

No interim analyses are planned.

Quality of Life Evaluations

The quality of life battery yields the following endpoints:

- FACT-An: Physical well being, Emotional well being, Social well being, Relationship with Doctor, Functional well being, Fatigue.
- Cancer Linear Analogue Scale: Energy, Activities, Overall Quality of Life.

These endpoints will be summarised by time point and treatment group. In addition, area under the curve (AUC) analysis will be performed using all endpoints to determine overall changes in mean Quality of Life level.

Null and Alternative Hypothesis

The null hypothesis is that mean Hemaglobin is equal for the two treatment groups. The alternative hypothesis is that the mean level of Hemaglobin is increased by 2.0 g/dL in adult ovarian patients receiving Epoetin alfa. Thus, the alternative hypothesis is one-sided.

Baseline Comparisons of Treatment Groups

Baseline comparability across treatment groups will be statistically assessed using Students' t-test. Pairwise treatment comparisons of screening visit demographics, laboratory and vital signs will be undertaken using this procedure. In addition, ECOG Performance Score, medical history, physical examination, chemotherapy/transfusion data, stage of solid tumours and concurrent therapy will be tabulated in an attempt to identify any trends over the treatment groups.

Safety Evaluations

The safety parameters to be evaluated are the incidence and severity of adverse events, laboratory tests (including haematology, serum chemistry, and iron profile), and vital sign measurements. All individual values will be listed. Vital parameters will be assessed descriptively. Laboratory values

will be compared to their reference ranges. The data will be transformed to standard international units as a basis for the evaluation The product specific WHO-ARD (World Health Organisation Adverse Reaction Dictionary) will be used for the coding of all adverse events reported. In addition, adverse events will be tabulated according to severity and will be categorised by event, body system and preferred term. No specific hypothesis will be tested with regard to the number of patients experienced an adverse event. All summaries will be based on the safety population, i.e. all subjects who are randomised and for whom assessments of safety parameters are available.

STUDY DRUG INFORMATION

Physical Description of Study Drug(s)

Epoetin alfa is a sterile, clear, colourless aqueous solution for injection, which will be provided in pre-filled, single-use syringes containing 10,000 IU/mL Epoetin alfa (a recombinant human erythropoietin) and 2.5 mg/mL human serum albumin in 1 mL of phosphate buffer. The activity of Epoetin alfa is determined by comparison of the product to the World Health Organisation (WHO) International Reference Standard #2 (10 IU/mL) by both bioassay and radioimmunoassay (RIA).

EXAMPLE 3

A RANDOMIZED STUDY TO EVALUATE THE EFFECT OF MAINTAINING HEMOGLOBIN LEVELS WITH EPOETIN ALFA, ON ANEMIA AND QUALITY OF LIFE IN BREAST CANCER SUBJECTS RECEIVING MYELOTOXIC CHEMOTHERAPY

SYNOPSIS

OBJECTIVES:

To evaluate the effect of Epoetin alfa treatment versus normal patient care (best supportive care), on Quality of life, in particular anemia and fatigue, in subjects with breast cancer who are undergoing **myelotoxic chemotherapy.** The primary endpoint will be Quality of Life scores for Anemia and Fatigue measured by the FACT-An anemia sub-scale at baseline after 4/6, 8/9,12 weeks of treatment and at study end.

OVERVIEW OF STUDY DESIGN:

This is a Phase IIIb randomised, open label, multicentre trial in 400 subjects. They will be randomly assigned in a 1:1 ratio to one of the two treatment arms, Epoetin alfa, 10,000 IU 3x/week, or conventional care. Subjects will continue to receive study medication until 4 weeks after the end of their last chemotherapy cycle. Chemotherapy Subjects will be randomised in to a group scheduled to receive epoetin alfa and a group with no epoetin alfa. Both groups will receive best supportive care according to the centre's normal practice.

Subjects will enter the trial and commence treatment with Epoetin alfa, as soon as their hemoglobin level reaches ≤12.0g/dL (7.44 mmol/L). The assumption is that worsening of anemia is a likely consequence of further chemotherapy and or the underlying disease. The aim of treatment is to maintain a hemoglobin level in the range 12.0 – 14.0 g/dL (7.44 – 8.68 mmol/L) therefore preventing symptomatic anemia and maintaining a good level of quality of life.

STUDY POPULATION:

The study will aim to include 400 subjects with a confirmed diagnosis of breast cancer (any stage), who are undergoing a myelotoxic chemotherapy regime, for at least 12 weeks, will be recruited.

DOSAGE AND ADMINISTRATION:

Subjects randomised to Epoetin alfa will receive either 10,000 IU Epoetin alfa, SC, 3x/week from a phosphate buffered pre-filled syringe formulation. Subjects randomised to the control group will receive identical treatment as they would were they not enrolled in a clinical trial, according to each individual centre's normal practices. Monthly hemoglobin level and or reticulocyte count will determine whether the same dose or an adjusted dose will be used for the remainder of the treatment.

EFFICACY EVALUATIONS/CRITERIA:

Main efficacy parameter:

- Difference in Quality of Life scores between the two study groups, measured with the FACT-An, anemia sub-scale after 12 weeks treatment.

Secondary efficacy parameters:

- Haematological response to Epoetin alfa, defined as an increase in hemoglobin from baseline,
  - Complete response, increase of ≥ 2 g/dL).
  - Partial haematological response, defined as an increase in hemoglobin of 1-1.99 g/dL from baseline.
  - Holding response, defined as an increase in hemoglobin of up to 0.99 g/dL from baseline combined with an increase in reticulocytes of > 40,000/µl
  - Treatment failure is defined as no change, or a fall in hemoglobin level from baseline associated with an increase in reticulocytes <40,000/µl.

- Difference in Quality of life scores between the study groups at the end of the trial (last on study visit) and for the complete trial period (AUC {area under the curve) for all assessments, as measured by the FACT AN, anemia subscale.
- Quality of life, energy levels and activity, derived from the Cancer linear Analogue Scale (measured at each visit and also by AUC for all assessments).
- Tumour Response to Chemotherapy.
- ECOG performance status.
- Frequency of blood transfusions.

SAFETY EVALUATIONS:
Assessment of laboratory tests, vital signs and incidence and severity of adverse events associated with study drug administration.

TIME AND EVENTS SCHEDULE:
The time and events schedule for this study is shown on the following page

TIME AND EVENTS SCHEDULE

	Pre-Treatment[A]	On-Study Visits				
Visit	1	2	3	4	5 Study completion (4 weeks after last chemotherapy) or earlier discontinuation	Follow up 6 & 12 months
Week of Study *	1	4-6*	8-9*	12	Up to 28	
Informed Consent	X[A]					
Medical History (incl. Previous chemotherapy)	X[A]					
Physical Examination	X[A]				X[D]	
Current Therapy	X					
Malignancy Staging	X[A]			X	X[D]	X
Laboratory Tests: **Haematology** - hemoglobin - haematocrit - reticulocyte count (optional) **Biochemistry** Transferrin	X[A] X[A]	X[B]	X[B]	X[B]	X[D]	
Vital Signs	X[A]	X[B]	X[B]	X[B]	X[D]	
ECOG Performance Score	X[A]			X[B]	X[D]	X
QoL Assessment - CLAS - FACT-An	X[C] X[C]	X[B] X[B]	X[B] X[B]	X[B] X[B]	X[D] X[D]	
Transfusion Data		X	X	X	X[D]	
Chemotherapy Data[C]	X	X	X	X	X[D]	
Tumour Response					X[D]	
Epoetin alfa dosing		X	X	X	X	
Concomitant therapy		X	X	X	X	
Adverse Events		X	X	X	X[D]	
Survival						X

* Variable according to either 3 or 4 weekly chemotherapy cycles. ** 4 weeks after end of chemotherapy
A. All procedures to be performed within 14 days of first study medication dose.
B. To be performed before start of next chemotherapy cycle.
C. All assessments must be done prior to administration of chemotherapy regimen.
D All procedures to be performed within 5 days after last dose of study medication.
F. Only Serious adverse events (SAE's).

OVERVIEW OF STUDY DESIGN

This is a Phase IIIb randomised multicentre trial in 400 adult, breast cancer subjects, aged older than 18 years, who are receiving myelotoxic chemotherapy. Subjects will be randomised in a 1:1 ratio to Epoetin alfa or no Epoetin alfa (control group, normal care). The subjects randomised to Epoetin alfa will receive Epoetin alfa, 10,000 IU or 5,000 IU if under 45 kg three times a week until on study chemotherapy cycles are complete. All subjects will receive best supportive care. Eligibility of all subjects will be determined by the inclusion and exclusion criteria listed in the following Sections.

Subjects should not have been transfused during the cycle of therapy before being enrolled in this study (last 14 days). Transfusions may be administered as necessary during the study.

The study population will comprise subjects who are at least mildly anaemic, Hb level ≤12.0 g/dL (7.44mmol/l). It is assumed that symptomatic anemia is a likely consequence of further chemotherapy and or the underlying disease. Study drug administration will start as soon as subjects have been randomised. For ease of operation it is advised that epoetin treatment be started at the beginning of the next chemotherapy cycle. This will allow accommodation of the study visit schedule without undue disturbance to the subjects planned clinic attendances.

STUDY POPULATION

General Considerations

400 breast cancer subjects, who are receiving myelotoxic chemotherapy or in whom such is planned, will be enrolled into the study as long they meet all the entry criteria. The specific inclusion and exclusion criteria for enrolling subjects in this study are described in the following sections.

Inclusion Criteria

Subjects must satisfy the following criteria to be eligible for the study:

1. Confirmed histological diagnosis of breast cancer.
2. Predicted to receive myelotoxic chemotherapy for at least 12 weeks, with or without co-administration of radiotherapy.
3. At least mild anemia at study entry, defined as a hemoglobin level ≤12.0 g/dL (7.44mmol/l).

4. An ECOG Performance Score of 0, 1 or 2.
5. A life expectancy of 6 months or longer, based on the investigator's clinical judgement.
6. Female subjects (note exclusion criteria) aged at least 18 years.
7. Subjects must have given their written informed consent, the nature of the study having been fully explained and a written information sheet having been provided.

Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from participating in the study:

1. Clinically significant disease/dysfunction of the pulmonary, cardio-vascular, endocrine (e.g. uncontrolled diabetes), neurological (e.g. uncontrolled or unexplained seizures), gastrointestinal, or genitourinary systems not attributable to underlying malignancy or chemotherapy.
2. Anemia due to factors other than cancer/radiotherapy/chemotherapy (e.g. haemolysis or gastrointestinal bleeding).
3. Active second primary malignancy or documented history of other malignancy within the last 3 years. With the exception of basal cell carcinoma of the skin or cervical cancer in situ.
4. Uncontrolled hypertension defined as a diastolic blood pressure greater than 95 mm Hg.
5. Presence of symptomatic, or untreated brain metastases.
6. Evidence of untreated iron, folate or Vitamin B_{12} deficiency.
7. Blood transfusion within 14 days prior to study entry.
8. Previous treatment, in the last 4 weeks, with epoetin alfa, or other licensed or experimental forms of erythropoietin.
9. Acute major illness within 7 days of study entry, or major infection within one month of study entry.
10. Surgery within 7 days prior to study entry.
11. Pregnant or lactating females or females of childbearing potential not currently practising a documented adequate method of contraception. (i.e, hormonal contraceptives, intrauterine device or barrier and spermicide). If a female subject is practising an acceptable method of birth control, she must continue with the same method during the entire study.
12. Participation in any other investigational drug trial or therapy, relating to anemia, within 30 days of randomisation. Or current inclusion in any other research project involving unlicensed or experimental

medications that would interfere with this study (experimental regimes involving licensed medications are permitted).

13. Known hypersensitivity to Epoetin alfa or one of its components.

RANDOMIZATION AND BLINDING

Overview

A central randomisation procedure will be used to avoid bias in the study. Subjects will be allocated to the two study groups in a 1:1 ratio upon satisfaction of the inclusion and exclusion criteria, completion of baseline questionnaires and clinical assessments.

Procedures

Subjects will be randomly allocated in a 1:1 ratio to receive initially either Epoetin alfa 10,000 IU 3x/week or conventional care. In order to randomise a subject the investigator or designee will be required to contact the central randomisation office. After confirmation of basic demographic and clinical information as well as key entry criteria, the subject will be allocated to a treatment group.

DOSAGE AND ADMINISTRATION

Clinical experience has indicated that Epoetin alfa in a dose of 150 IU/kg SC 3x/wk can correct anemia in cancer subjects receiving chemotherapy. A fixed dose of 10,000 IU corresponds to 150 IU/kg in a subject having a body weight of approximately 70 kg.

Initial Dosage

Study medication will be provided in pre-filled, single-use 1mL syringes, containing 10,000 IU Epoetin alfa and will be administered by subcutaneous injection three times a week on a basis appropriate to the subject's situation. Each dose should be separated by at least two days, i.e. dose on Monday, Wednesday, and Friday.

Subjects will receive as a starting dose, 10,000 IU of Epoetin alfa three times a week.

DOSAGE VARIATIONS

For Subjects with a body weight < 45 kg, the following adjustments will be made:

- Subjects < 45 kg: Subjects will be given a fixed dose of 5,000 IU. s.c. t.i.w. For this purpose single use pre-filled syringes containing 4000 IU and 1000 IU Epoetin alfa will be provided. Alternatively half a 10,000 IU pre-filled syringe may be administered.

Dosage Adjustments

The initial dose will be maintained through the first on-study chemotherapy cycle (4 weeks) for 4 week cycles and through 2 cycles (6 weeks) for 3 week cycles. If at the end of Week 4/6* the reticulocyte count has not increased by > 40,000/μL or the Hb has not increased by > 1 g/dL above baseline, the dose of Epoetin alfa is to be increased to 20,000 IU (300 IU/kg) S.C. t.i.w.starting at the week 5/7* dose. For Subjects with a body weight < 45 kg, the dose of Epoetin alfa should be increased to 10,000 IU. s.c. t.i.w.

(* 4/3 week cycles respectively)

Subjects should continue on Epoetin alfa until 4 weeks after the end of their last chemotherapy cycle.

If at any time the hemoglobin exceeds 14 g/dL (8.69 mmol/L), the study medication must be withheld until the hemoglobin has fallen below 12.5 g/dL (7.75 mmol/L), and will then be restarted at a dose 33 % lower than the dose previously administered (dependent on the rate of increase). This may be achieved by omitting one of the week's doses, dosing then being 10,000 IU. s.c. b.i.w.

If the hemoglobin is rising by ≥ 2 g/dL (1.24 mmol/L) per month or 1.5 g/dL (0.93mmol/L) after 3 weeks, the dose of the study medication will be reduced by 33% to maintain the rate of increase of hemoglobin to < 2 g/dL per month. This may be achieved by omitting one of the weeks doses, dosing then being 10,000 IU. s.c. b.i.w.

Do not adjust the Epoetin alfa dose if the increase in hemoglobin is due to a transfusion.

Subjects will be instructed by the investigator or the responsible study nurse on the correct administration technique and schedule for the study medication. The subject has to demonstrate his/her competence to administer self-injections, if this is planned. The Local sponsor will provide instructional material in the subjects' language on the use of pre-filled syringes.

The study medication is to be administered by subcutaneous injection. Each syringe of study medication should be used only once.

CONCOMITANT THERAPY

Note: The use of licensed white cell growth factors is allowed during the study.

All concomitant therapy being administered at the time of onset, and during the course, of any Serious Adverse Event (SAE) must be reported in the case report form. Concomitant medication associated with cancer treatment or symptom management will not be collected.

Iron supplementation should be given to maintain appropriate iron availability and iron stores so that erythropoiesis is not restricted. A daily dose of 200 mg of elemental iron as oral iron supplementation is recommended. Transferrin saturation > 20% will be considered as indication of adequate iron stores.

Red Cell Transfusions may be administered when clinical judgement deems necessary during the study, but every effort will be made not to transfuse subjects until their hemoglobin is below 9 g/dL (5.58 mmol/L).

If chemotherapy, is discontinued, the subject may continue on Epoetin alfa therapy for up to a total of 4 weeks after the last dose of chemotherapy. At the time treatment is discontinued, the following evaluations must be completed.

- Clinical laboratory tests: Hemoglobin.
- Reason for chemotherapy discontinuation.

If possible the subject should be asked to complete the QoL questionnaires (FACT An/CLAS) which comprise the final visit.

In case of a serious adverse event (SAE), all concomitant therapy administered at the time of onset of the SAE must be reported in the case report form.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

STUDY PROCEDURES

Overvi w

The Time and Events Schedule included in the synopsis summarizes the frequency and timing of the safety and efficacy measurements.

The study is divided into visits with associated evaluations and procedures, which must be performed at the specified time points, as described in the following Sections. A flow chart of the study is provided in the Time and Events Schedule (Synopsis).

Subjects will be evaluated for entry criteria during a screening period of up to 14 days prior to the start of study treatment. When found eligible for the trial, they will be randomised.

Screening Period

The following procedures will have been completed for each subject within the 14 days prior to administration of the study medication.

✓ Informed consent.

N.B. Informed consent must be obtained before any procedures are carried out which do not form a part of the subject's normal care or are specifically carried out in order to establish eligibility.

✓ Medical history, including chemotherapy (number of cycles, drugs and dosage) for the

preceding 4 weeks, and Hb level at the beginning of the current cycle of chemotherapy.

✓ Vital signs, physical examination and symptoms of malignant disease.

✓ History and staging of malignancy[3].

✓ ECOG performance score, as determined by investigator.

✓ Information on previous anticancer therapy, including surgery for the past 4 weeks.

✓ <u>Haematology</u>

➢ hemoglobin[4]

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[3] Where ever possible, the TNM system for staging of solid tumours should be used (see attachment 5).

For the purpose of this study, baseline screening measurements for haematology to establish eligibility may be obtained from the clinical records of the prospective subjects, provided they form part of the normal clinical management of the patient

- Haematocrit
- Total erythrocyte (RBC) count
- Total leukocyte (WBC) count
- Platelet count
- Reticulocyte count (μL^{-1}) (according to local practice)

✓ **Iron status**:

In order to assess the patient's iron stores at study entry appropriate laboratory tests should have been made. For example serum iron, ferritin, total iron binding capacity or calculation of transferrin saturation. Although not recorded in the CRF, evidence confirming the patient's iron status should be present in their clinical records.

Study Entry (baseline data)

If the subject is qualified to participate in the study, the following items should be completed just before formal randomisation.

The subject should complete the Quality of Life (QoL) questionnaires: FACT-An sub-scale and Cancer Linear Analogue Scale. Subjects should be unaware of any of their haematology results prior to completion of the questionnaires. After completion of the FACT An questionnaire, patients will be asked to indicate which item out of the questionnaire is of greatest importance to them and therefore that which would be most desirable for the treatment to improve.

Study drug administration may be started as soon as entry criteria are satisfied, in particular with regard to hemoglobin level (inclusion no 3). For ease of operation it is advised that epoetin treatment be started at the beginning of the next chemotherapy cycle. This will allow accommodation

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4 This Hb level measured within seven days of study entry is defined as the baseline Hb for evaluating response to study medication

of the study visit schedule without undue disturbance to the subjects planned clinic attendances.

Treatment

During treatment phase, subjects are required to visit the investigator's office or clinic at the end of each chemotherapy cycle, i.e. just before starting the next chemotherapy cycle. . During treatment with epoetin alfa (Eprex/Erypo) a gradual increase of hemoglobin of up to 2g/dL/month is recommended. In order to ensure this, it is recommended that hemoglobin is monitored regularly (up to once/week) until the increase in hemoglobin is stable. Thereafter hemoglobin should be monitored periodically (at least monthly). This should be achieved in concord with the treating clinician's judgement, the patients treatment plan and associated clinic attendances. Hemoglobin levels will be recorded in the CRF at the end of selected chemotherapy cycles.

During the study visits (coinciding with the end of a chemotherapy cycle), i.e. just before starting the next chemotherapy cycle, the following data and information will be collected and registered in the individual Case Report Form:

- ✓ Details of each Epoetin alfa administration: dates and doses.
- ✓ Haematology (Hb, Hct, Retic).
- ✓ Changes in chemotherapy schedule.
- ✓ Transfusion information, including Hb level prior to transfusion, volume and type of product transfused (after each chemotherapy cycle).
- ✓ Occurrence of adverse event (at each visit).
- ✓ Evaluation of vital signs.
- ✓ ECOG performance score.
- ✓ **Quality of Life questionnaire: FACT An and Cancer Linear Analogue Scale after 4 or 6*, 8 or 9* and 12 weeks of epoetin alfa treatment**

STUDY TERMINATION

A study termination visit will be scheduled within 5 days of last dose of study medication or upon premature withdrawal from the study. Study medication

will be continued for 4 weeks after the end of chemotherapy. The following procedures will be performed:

- ✓ Physical examination including vital signs measurements, and any current clinical signs and symptoms of malignant disease.
- ✓ Quality of Life questionnaire: Cancer Linear Analogue Scale. FACT An anemia sub-scale.
- ✓ Tumour response to chemotherapy.
- ✓ Haematology tests.
- ✓ Transfusion information, including Hb level prior to transfusion, volume and type of product transfused.
- ✓ Possible occurrence of adverse events.
- ✓ Details of chemotherapy and or radiotherapy.
- ✓ ECOG performance score, as determined by the investigator.

DISCONTINUATION OF ANTI-CANCER TREATMENT

If the current regime of anti-cancer treatment (chemotherapy and /or radiotherapy, the subject may continue on Epoetin alfa therapy until 4 weeks after the end of the last chemotherapy cycle or radiotherapy dose. At the time anti-cancer treatment is discontinued, the following evaluations must be completed.

- ✓ Clinical laboratory tests: Hemoglobin, routine haematology.
- ✓ Tumour response to chemotherapy. Longer term (up to 6 months) follow up may be implemented, but will not require further study visits.
- ✓ Reason for chemotherapy discontinuation.

FOLLOW UP ASSESSMENT

All patients entered will be followed up after 6 and 12 months after the study start date. This will not necessarily require a formal study visit, as the information required will be simply whether the patient is still alive. If the patient has died in the intervening period, the date of death will be required. These data will be analysed separately to the main study.

STUDY EVALUATIONS

Primary parameter

The primary efficacy parameter will be quality of life after 12 weeks treatment, measured by decrease in FACT-AN sub-scale scores from baseline. This will be analysed for all patients who have completed at least 8 weeks of treatment (and therefore can provide 2 data points). The FACT-An will be administered at entry, after 4/6, 8/9, 12 weeks and at study completion or early termination.

The complete quality of life battery, composed of the FACT-An sub-scale and the Cancer Linear Analogue Scale, is self-administered by the subject and addresses issues of functioning, well-being and specific fatigue experiences. The questionnaires should always be completed in the same order, i.e., starting with the FACT-An, then the Cancer Linear Analogue Scale. Subjects should be unaware of any of the haematology results prior to completion of the questionnaires.

Secondary parameters

Secondary parameters include the following

HAEMATOLOGICAL RESPONSE

A Complete haematological response is defined as an increase in hemoglobin of 2.0g/dl or more from baseline. Patients who achieve a hemoglobin level >14.0 g/dl at any time during treatment will also be regarded as having demonstrated a complete response.

A partial haematological response, will be defined as an increase in hemoglobin of 1-1.99 g/dL from baseline, whilst a holding response, will be defined as an increase in hemoglobin of up to 0.99 g/dL from baseline baseline combined with an increase in reticulocytes of > 40,000/μl.

Treatment failures are non-responders, defined as either no change or a fall in hemoglobin level, from baseline accompanied by an increase in reticulocytes < 40,000/μl. Non-responders will also include those with a hemoglobin increase that have received blood transfusion within the preceding four weeks.

QUALITY OF LIFE (CLAS)

Quality of life, Energy levels and activity as measured by the Cancer Linear Analogue Scale (CLAS) will be recorded at each study visit.

QUALITY OF LIFE (FACT – AN)

Quality of life throughout the complete study period will be measured by answers to the FACT-AN anemia sub-scale measured at baseline, 12 weeks and study completion or early discontinuation. This will involve comparison of the area under the curve (AUC) for QoL scores between the two groups.

ECOG PERFORMANCE SCORE

ECOG performance status will be assessed at entry, 8-9 weeks, 12 weeks and at study completion.

TUMOUR RESPONSE TO CHEMOTHERAPY.

Tumour response to chemotherapy will be assessed at the time of study completion.

OVERALL SURVIVAL

Overall patient survival will be recorded 6 and 12 months after the start of the study. These data will be analysed outside of the main study.

Other assessments

INCIDENCE OF BLOOD TRANSFUSIONS

The number of allogenic blood transfusions will be recorded for all patients during the treatment period.

SUBJECT COMPLETION

Completion

A subject will be classified as having completed the study if he/she has completed study medication as described herein 6 and has had all evaluations completed at appropriate visits including Study Termination visit. Subjects should complete at least 12 weeks of chemotherapy while taking study medication. Up to 6 chemotherapy cycles plus 4 weeks (22-28 weeks) are allowed during study participation.

Withdrawal

Subject participation may be terminated prior to completing the study for any of the following reasons:

- Adverse Event
- Subject choice
- Lost to follow-up
- Other

Subjects who withdraw should have the procedure performed as prescribed for the Study Termination visit.

Additionally, the investigator is to retrieve all remaining study drug containers, whether empty or containing drug.

When a subject withdraws prior to completing the study, the reason for withdrawal is to be documented on the CRFs and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced.

STATISTICAL METHODS

The analysis of the data will be the responsibility of Janssen-Cilag, European Medical Affairs and will be carried out by the biostatistics department of ACIS, Athens, Greece.

In this chapter only the most important aspects of the statistical analysis are described. These sections were copied from the corresponding sections of the detailed statistical analysis plan (SAP) which has been written and authorized at the same time as this protocol. The SAP is an official internal Janssen-Cilag, European Medical Affairs document and is available on request only.

Study Population

The number of subjects, who were enrolled, and treated and who completed each visit (± allowed time frame) of study will be tabulated by center and country as well as overall/combined. Furthermore, a graphical presentation of the disposition of subjects by center and country will be given.

PROTOCOL VIOLATIONS

All protocol violations will be determined by medical, clinical and biometrics personnel and will be reported by center and country.

SUBJECTS DATA SETS

All-subject-Treated Group (AST)

The All-Subjects-Treated (AST) group consists of all subjects, who received at least one dose of in-treatment study medication. In cases where all dispensed study medication was returned (per investigator's record), the subject will be considered as non-treated, and will be excluded from the AST-group.

Intent to Treat Group (ITT)

The Intent to Treat Group (ITT) group consists of all subjects from the AST-group, who had at least one post-baseline assessment of the primary variable.

Per Protocol Group (PP)

The Per Protocol Group (PP) group consists of all subjects from the ITT-group, without any major protocol violation.

Efficacy Evaluations

PLANNED ANALYSES

All efficacy and safety parameters will be presented descriptively. Tables of descriptive statistical parameters (number of non-missing values, mean, standard deviation, median, range) and/or frequency tables (n, %) will be constructed for each time point.

Primary Efficacy Parameter

The main objective of this study will be to compare differences in Quality of life between the two groups after 12 weeks, according to the FACT (Functional Assessment of Chronic Illness Therapy) - Anemia subscale Total Score.

The primary analysis of the main variable will be based on intention-to-treat population. The per-protocol analysis will be considered as secondary analysis.

Analysis of primary variable will be based on a linear mixed-effect model with treatment group as the exploratory variet of primary interest. Fitting will be performed using SAS PROC MIXED. The likelihood ratio statistic will be used to assess the treatment difference. Effects of the covariates on the primary variable will be assessed similarly. Except from covariets, centre effect will be fitted if adequate number of patients (≥8) will be enrolled in each investigational site. The covariance structure used will be that of a first order autoregressive structure, which implies that the stochastic dependence among repeated responses is decreasing geometrically with distance between them.

The Functional Assessment of Chronic Illness Therapy Anemia scale is multilingual validated scale composed of three scales:

- Fact-G
- Fact-F

➢ Fact-non F

This trial will use the anemia subscale (FACT-F + FACT-non F) as a stand-alone instrument. The FACT scales are designed for patient self-administration, but can also be administered by interview format. For self-administration, subjects should be instructed to read the brief directions at the top of the page. After the subject's correct understanding has been confirmed, he/she should be encouraged to complete every item in order without skipping any. Some subjects may feel that a given question is not applicable to them, and will therefore skip the item altogether. **Subjects should be encouraged to circle the response that is most applicable.**

SCORING THE SCALE

Handling missing data: If there are missing items, subscale scores can be prorated. This is done by multiplying the sum of subscale by the number of items in the subscale, then dividing by the number of items actually answered. This can be done using the formula below:

$$\frac{\sum a_i \times N}{n}$$

where a_i is an item score, N the number of items in the subscale and n the number of items answered. When there are missing data, prorating by subscale in this way is acceptable as long as **more than** 50% of the items were answered (i.e., a minimum of 4 of 7 items, 4 of 6 items, etc.). The total score is then calculated as the sum of the unweighted subscale score.

Handling missing questionnaires: If there are missing questionnaires, missing scores will be replaced with estimated values. That is, middle random missing values will be imputed using the linear interpolation of the two adjacent measurements. Missing values resulting at the end of the time profiles will be replaced with the last available value of the visit for that patient, assuming a constant score over time. In a different case, other methods (regression imputation, multiple imputation) will be applied.

Scoring specific scale: The total score for the Fact-An "Additional concern" subscale is composed of two subscales, the Fatigue items and non-Fatigue items which together are the Anemia items (20 in total). Over 50% must be completed in order to consider the subscale score valid.

Secondary Efficacy Parameter

Secondary efficacy parameters are will be defined as follow:

a. Total Anemia/fatigue subscale score between end of trial and baseline, measured by AUC;

b. Change in the CLAS between end of trial and baseline;

c. Change in the Hemoglobin values between baseline and different visits.

d. Change in ECOG performance status

e. Tumour response to chemotherapy

f. Overall subject survival will be presented as a Kaplan-Meier plot. A log-rank test will be carried out by way of confirmatory analysis.

Analyses of the secondary endpoints of the trial will employee much the same techniques as that of the primary analysis. Mixed-effect models will be fitted for the evaluation of treatment effect with respect to total anemia/fatigue sub-scale score and CLAS. Change in the Hemoglobin values between baseline and different visits will be assessed by use of analysis of covariance (ANCOVA). Finally, ECOG performance status and tumour response will be tabulated according to treatment regimen and compared descriptively. Whenever it is considered necessary, Wilcoxon rank-sum test will be applied.

Other assessments

Incidence of allogenic blood transfusion will be tabulated and presented in relation to hemoglobin level, and tumour staging.

SAFETY EVALUATIONS

Changes from baseline in physical examinations will be tabulated according to treatment group. Vital signs will be assessed by means of descriptive statistical analysis. All adverse events will be coded using the WHO-Adverse Reaction Terminology List. Evaluations of the adverse events will be based on the body system and preferred term. Adverse events will be tabulated according to intensity and drug relationship. The frequencies and incidences of adverse events after treatment with the trial drugs will be presented. No specific hypothesis will be tested with regard to the number of patients experienced an adverse event. Laboratory values will be compared to their reference ranges and shift tables will be constructed for each treatment group. In addition, summary statistics will be provided.

13.2.3. BASELINE COMPARABILITY OF TREATMENT GROUPS

Descriptive univariate statistics (mean, median, standard deviation, minimum, maximum or percentages) will be used to evaluate baseline comparability between the two treatment groups. No confirmatory statistical tests will be applied. Variables appeared to have baseline differences between treatment arms will be fitted as covariates in the mixed-effect model and analysis of covariance.

1.1.4. SAMPLE SIZE DETERMINATION

The sample size is calculated based on the comparison of the change of QoL from baseline to 12 weeks between non-treated subjects and patients receiving Epoetin alfa. Based on a two-sided test of statistical significance

and a random assignment to one of the two treatment arms in a 1:1 ratio, a sample size of 170 patients per treatment group will be sufficient to detect, with power 80% and 0.05 significance level, a mean difference of 12% assuming that the common standard deviation is 12. A drop-out rate estimate of about 15% will yield a total sample size of 400 randomised subjects.

INTERIM ANALYSIS

No interim analyses are planned. However, it is planned to analyse the survival data, obtained from follow-up assessments, separately to the main body of the study. This will allow the core quality of life data to be analysed expediently.

STUDY DRUG INFORMATION

Physical Description of Study Drug(s)

Epoetin alfa is a sterile, clear, colourless aqueous solution for injection, which will be provided in pre-filled, single-use syringes containing 10,000 IU/mL Epoetin alfa (a recombinant human erythropoietin) in 1 mL of phosphate buffer. The activity of Epoetin alfa is determined by comparison of the product to the World Health Organisation (WHO) International Reference Standard #2 (10 IU/mL) by both bioassay and radioimmunoassay (RIA).

EXAMPLE 4

A CLINICAL EVALUATION OF EPOETIN ALFA IN ANEMIC CANCER PATIENTS RECEIVING PLATINUM BASED CHEMOTHERAPY

SYNOPSIS

OBJECTIVES:

To evaluate the effectiveness, safety, and clinical outcomes of Epoetin alfa in the treatment of anaemic cancer patients receiving platinum based chemotherapy. The primary aim is to compare the degree of anemia as indicated by hemoglobin level, with the subject's quality of life. The endpoints will therefore be:

- Improvement in the subjects Quality of Life as measured by the FACT-An scale and the Cancer Linear Analogue Scale. This will be related to hemoglobin level evaluated at each study visit.
- Haematological response to Epoetin alfa.
- Assessment of the safety of Epoetin alfa when used in the treatment of anemia during platinum-based chemotherapy.

OVERVIEW OF STUDY DESIGN:

This is a Phase IV, open label, multicentre trial in 1000 subjects. All subjects will be assigned to receive Epoetin alfa, 150 IU/kg (10,000 IU) 3x/week. Subjects may receive study medication until 4 weeks after the last dose of chemotherapy or up to a maximum of 28 weeks.

STUDY POPULATION:

1000 subjects with confirmed diagnosis of malignancy (any stage), receiving platinum-containing chemotherapy for at least 8 weeks (two or more chemotherapy cycles).

Subjects will be at least mildly anaemic having a hemoglobin level at entry of ≤12.0g/dL (7.44 mmol/l). The assumption is that worsening of anemia is a likely consequence of further chemotherapy and or the underlying disease.

DOSAGE AND ADMINISTRATION:

Subjects will receive either 150 IU/kg or 10,000 IU Epoetin alfa, SC, 3x/week from a phosphate buffered pre-filled syringe formulation. Monthly reticulocyte count and/or hemoglobin level will determine whether the same dose or an adjusted dose will be used for the remainder of the treatment.

EFFICACY EVALUATIONS/CRITERIA:

Main efficacy parameter:

- Improvement in Quality of Life from baseline as measured by decrease in mean FACT-An score for all patients.

Secondary efficacy parameters:

- Quality of life, Energy levels and activity as measured by the Cancer Linear Analogue Scale (CLAS).
- Haematological response to Epoetin alfa, defined as an increase in hemoglobin from baseline,
  - Complete response increase of ≥ 2 g/dL , w).
  - Partial haematological response, defined as an increase in hemoglobin of 1-1.99 g/dL from baseline
  - Holding response, defined as an increase in hemoglobin of up to 0.99 g/dL from baseline combined with an increase in reticulocytes of > 40,000/µl
  - Treatment failure is defined as no change, or a fall in hemoglobin level from baseline associated with an increase in reticulocytes <40,000/µl.
- ECOG performance score
- Tumour response to chemotherapy.

OTHER ASSESSMENTS:
Incidence of blood transfusion.

SAFETY EVALUATIONS:
Assessment of laboratory tests, vital signs and incidence and severity of adverse events associated with study drug administration.

TIME AND EVENTS SCHEDULE:
The time and events schedule for this study is shown on the following page

TIME AND EVENTS SCHEDULE

Visit	Pre-Treatment[A]	On-Study Visits			Follow up (optional continuation of Epoetin treatment until 4 weeks after last chemotherapy)
	1	2	3	4 (Study Completion or Early Termination) [E]	
Week of Study *	1	4-6*	8-9*	12	Up to 28
Informed Consent	X				
Medical History (incl. Previous chemotherapy)	X				
Physical Examination	X			X	
Current Therapy	X				
Malignancy Staging	X			X	X
Laboratory Tests: **Haematology** - hemoglobin - haematocrit - reticulocyte count (optional)	X	X[B]	X[B]	X[B]	X
Vital Signs	X	X[B]	X[B]	X[B]	
ECOG Performance Score	X	X[B]	X[B]	X[B]	X
QoL Assessment - CLAS - FACT-An	X X	X[B]	X X	X[B] X[B]	
Transfusion Data		X	X	X	
Chemotherapy Data[C]	X	X	X	X	
Tumour Response				X	X
Epoetin alfa dosing		X	X	X	X
Concomitant therapy		X	X	X	
Adverse Events[D]		X	X	X	X[F]

* Variable according to either 3 or 4 weekly chemotherapy cycles. ** 4 weeks after end of chemotherapy
A. All procedures to be performed within 7 days of first study medication dose.
B. To be performed before start of next chemotherapy cycle.
C. All assessments must be done prior to administration of chemotherapy regimen.
D. Including concomitant therapy.
E. All procedures to be performed within 5 days after last dose of study medication.
F. Only Serious adverse events (SAE's).

OBJECTIVES

To assess the effect of early intervention and/or treatment with Epoetin alfa on anemia in adult cancer subjects receiving platinum containing chemotherapy. The main endpoint will be improvement in the subjects Quality of Life as measured by the FACT-An scale. Secondary end points will include: change in hemoglobin level; levels of activity, energy and quality of life measured with the Cancer linear analogue scale; ECOG performance status; Tumour response to chemotherapy..

OVERVIEW OF STUDY DESIGN

This is a Phase IV single arm, open, multicentre trial in 1000 adult cancer subjects aged older than 18 years who are receiving platinum containing chemotherapy. Subjects will receive 150 IU/kg of Epoetin alfa (10,000 IU or 5,000 IU if under 45 kg) three times a week until on study chemotherapy cycles are complete. Eligibility of all subjects will be determined by the inclusion and exclusion criteria listed in the following Sections.

Subjects should not have been transfused during the cycle of therapy before being enrolled in this study (last 14 days). Transfusions may be administered as necessary during the study. Based on clinical judgement, every effort should be made not to transfuse subjects who have an Hb > 9 g/dL.

The study population will comprise subjects who are at least mildly anaemic, Hb level ≤12.0 g/dL (7.44mmol/l) and assumes that worsening of anemia is a likely consequence of further chemotherapy and or the underlying disease. Study drug administration may start as soon as entry criteria have been satisfied. For ease of operation it is advised that epoetin treatment be started at the beginning of the next chemotherapy cycle. This will allow accommodation of the study visit schedule without undue disturbance to the subjects planned clinic attendances.

STUDY POPULATION

General Considerations

1000 cancer subjects receiving platinum-containing chemotherapy, who meet the following criteria on pre-study examination, will be enrolled into the study. The specific inclusion and exclusion criteria for enrolling subjects in this study are described in the following sections.

Inclusion Criteria

Subjects must satisfy the following criteria to be eligible for the study:

1. Confirmed diagnosis of cancer, for which platinum based chemotherapy is underway or imminent.
2. Predicted to receive further chemotherapy for at least 8 weeks.
3. At least mild anemia at study entry, defined as a hemoglobin level ≤12.0 g/dL (7.44mmol/l).
4. An ECOG Performance Score of 0, 1, 2, or 3.

5. A life expectancy of 3 months or longer, based on the investigator's clinical judgement.
6. Aged at least 18 years.
7. Male or Female subjects (see exclusion criteria).
8. Subjects must have given their written informed consent, the nature of the study having been fully explained and a written information sheet having been provided.

Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from participating in the study:

1. Clinically significant disease/dysfunction of the pulmonary, cardio-vascular, endocrine, neurological, gastrointestinal, or genitourinary systems not attributable to underlying malignancy or chemotherapy.
2. Uncontrolled hypertension defined as a diastolic blood pressure greater than 95 mm Hg.
4. A history of seizures.
5. Previous treatment in the last 2 months with epoetin alfa, licensed or investigational forms of erythropoetin.
6. Evidence of untreated iron, folate or Vitamin B_{12} deficiency.
7. Blood transfusion within 14 days prior to study entry.
8. Anemia due to factors other than cancer/radiotherapy/chemotherapy (haemolysis or gastrointestinal bleeding).
9. Acute major illness within 7 days of study entry, or any unresolved major infection.
10. Planned bone marrow or periferal stem cell transplant during the study period.
11. Surgery within 7 days prior to study entry.
12. Pregnant or lactating females or females of childbearing potential not currently practising a documented adequate method of contraception. (i.e, hormonal contraceptives, intrauterine device or barrier and spermicide). If a female subject is practising an

acceptable method of birth control, she must continue with the same method during the entire study.

13. Participation in any other investigational drug trial or therapy, relating to anemia, within 30 days of entry. Or current inclusion in any other research project involving unlicensed medications or procedures, which would interfere with this study.

14. Known hypersensitivity to Epoetin alfa or one of its components.

RANDOMIZATION AND BLINDING

Overview

This is a single arm, open trial and so no randomisation is involved.

DOSAGE AND ADMINISTRATION

Clinical experience has indicated that Epoetin alfa in a dose of 150 IU/kg SC 3x/wk can correct anemia in cancer subjects receiving platinum chemotherapy. A fixed dose of 10,000 IU corresponds to 150 IU/kg in a subject having a body weight of 70 kg.

Initial Dosage

Study medication will be provided in pre-filled, single-use 1mL syringes, containing 10,000 IU Epoetin alfa and will be administered by subcutaneous injection three times a week on a basis appropriate to the subject's situation. Each dose should be separated by at least two days, i.e. dose on Monday, Wednesday, and Friday.

Subjects will receive as a starting dose, 150 IU/kg (10,000 IU) of Epoetin alfa three times a week.

DOSAGE VARIATIONS

For Subjects with a body weight < 45 kg, the following adjustments will be made:

- Subjects < 45 kg: Subjects will be given a fixed dose of 5,000 IU. s.c. t.i.w. For this purpose single use pre-filled syringes containing 4000 IU and 1000 IU Epoetin alfa will be provided. Alternatively half a 10,000 IU pre-filled syringe may be administered.

Dosag Adjustm nts

The initial dose will be maintained through the first on-study chemotherapy cycle (4 weeks) for 4 weekly cycles and through 2 cycles (6 weeks) for 3 weekly cycles. If at the end of Week 4/6 the reticulocyte count has not increased by > 40,000/μL or the Hb has not increased by > 1 g/dL above baseline, the dose of Epoetin alfa is to be increased to 20,000 IU (300 IU/kg) S.C. t.i.w.starting at the week 5/7* dose. For Subjects with a body weight < 45 kg, the dose of Epoetin alfa should be increased to 10,000 IU. s.c. t.i.w.

(* 4/3 weekly cycles respectively)

Subjects should continue on Epoetin alfa until 4 weeks after the end of their last chemotherapy cycle.

If at any time the hemoglobin exceeds 14 g/dL (8.69 mmol/L), the study medication must be withheld until the hemoglobin has fallen below 12 g/dL (7.45 mmol/L), and will then be restarted at a dose 25–50 % lower than the dose previously administered. This will be dependent on the rate of increase. This may be achieved by omitting one of the week's doses, dosing then being 10,000 IU. s.c. b.i.w.

If the hemoglobin is rising by ≥ 2 g/dL (1.24 mmol/L) per month, the dose of the study medication will be reduced by 25-50% to maintain the rate of increase of hemoglobin to < 2 g/dL per month. This will be dependent on the rate of increase. This may be achieved by omitting one of the weeks doses, dosing then being 10,000 IU. s.c. b.i.w.

Do not adjust the Epoetin alfa dose if the increase in hemoglobin is due to a transfusion.

Subjects will be instructed by the investigator or the responsible study nurse on the correct administration technique and schedule for the study medication. The subject has to demonstrate his/her competence to administer self-injections, if this is planned. The Local sponsor will provide instructional material in the subjects' language on the use of pre-filled syringes.

The study medication is to be administered by subcutaneous injection. Each syringe of study medication should be used only once.

COMPLIANCE

Subjects will be instructed to return all unused medication containers to the investigator. The investigator will keep a detailed inventory of all study medication received, dispensed and returned. Drug supplies for each subject will be inventoried and accounted for throughout the trial.

CONCOMITANT THERAPY

Note: The use of licensed white cell growth factors is allowed during the study.

All concomitant therapy being administered at the time of onset, and during the course, of any the SAE must be reported in the case report form. Other concomitant medication associated with cancer treatment or symptom management will not be collected.

Iron supplementation should be given to maintain appropriate iron availability and iron stores so that erythropoiesis is not restricted. A daily dose of 200 mg of elemental iron as oral iron supplementation is recommended. Transferrin saturation > 20% will be considered as indication of adequate iron stores.

Red Cell Transfusions may be administered when clinical judgement deems necessary during the study, but every effort will be made not to transfuse subjects until their hemoglobin is below 9 g/dL (5.58 mmol/L).

If chemotherapy is discontinued, the subject may continue on Epoetin alfa therapy for up to a total of 4 weeks after the last dose of chemotherapy. At the time chemotherapy is discontinued, the following evaluations must be completed.

- Clinical laboratory tests: Hemoglobin.
- Reason for chemotherapy discontinuation.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

STUDY PROCEDURES

Overview

The Time and Events Schedule included in the synopsis summarizes the frequency and timing of the safety and efficacy measurements.

The study is divided into visits with associated evaluations and procedures, which must be performed at the specified time points, as described in the following Sections. A flow chart of the study is provided in the Time and Events Schedule (Synopsis).

Subjects will be evaluated for entry criteria during a screening period of 7 days prior to study treatment start.

Screening Period

The following procedures will have been completed for each subject within the 7 days prior to administration of the study medication.

- Informed consent. *N.B. Informed consent must be obtained before any procedures are carried out which do not form a part of the subject's normal care or are specifically carried out in order to establish eligibility.*
- Medical history, including planned chemotherapy (number of cycles, drugs and dosage), and Hb level at the beginning of the current cycle of chemotherapy.
- Vital signs and any symptoms of malignant disease.
- History and staging of malignancy[5].

<u>Haematology</u>:

- hemoglobin[6] - ***For the purpose of this study, baseline screening measurements for haematology to establish eligibility may be obtained from the clinical records of the prospective subjects, provided they form part of the normal clinical management of the patient***
- * Haematocrit
- * Reticulocyte count (μL^{-1}) (optional according to local practice)

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[5] Where ever possible, the TNM system for staging of solid tumours should be used. Information will be provided in the study support materials to describe the TNM staging of all tumour types. For other tumour types, the investigator may use an appropriate and internationally acceptable staging system of his own choice.

[6] This Hb level measured within seven days of study entry is defined as the baseline Hb for evaluating response to study medication

- Iron status: Appropriate assessment should be made of a subjects iron status, subjects should not have untreated iron deficiency (see exclusion criteria).

- ECOG performance score, as determined by investigator.

Study Entry (baseline data)

If the subject is qualified to participate in the study, the following items should be completed just before medication is started.

The subject should complete the Quality of Life (QoL) questionnaires: FACT An and Cancer Linear Analogue Scale. Subjects should be unaware of any of the haematology results prior to completion of the questionnaires. After completion of the FACT An questionnaire, patients will be asked to indicate which item out of the additional concerns section (last 20 questions) is of greatest importance to them and therefore that which would be most desirable for the treatment to improve.

Study drug administration may be started as soon as entry criteria are satisfied. For ease of operation it is advised that epoetin treatment be started at the beginning of the next chemotherapy cycle. This will allow accommodation of the study visit schedule without undue disturbance to the subjects planned clinic attendances.

Treatment

During treatment phase, subjects are required to visit the investigator's office or clinic at the end of each chemotherapy cycle, i.e. just before starting the next chemotherapy cycle. . During treatment with epoetin alfa (Eprex/Erypo) a gradual increase of hemoglobin of up to 2g/dL/month is recommended. In order to ensure this, it is recommended that hemoglobin is monitored regularly (up to once/week) until the increase in hemoglobin is stable. Thereafter hemoglobin should be monitored periodically (at least monthly). This should be achieved in concord with the treating clinician's judgement, the patients treatment plan and associated clinic attendances. Hemoglobin levels will be recorded in the CRF at the end of selected chemotherapy cycles.

During the study visits (coinciding with the end of a chemotherapy cycle), i.e. just before starting the next chemotherapy cycle, the following data and information will be collected and registered in the individual Case Report Form:

- Details of each Epoetin alfa administration: dates and doses.
- Haematology (Hb, Hct, Retic[optional]).

- Changes in chemotherapy schedule.
- Transfusion information, including Hb level prior to transfusion, volume and type of product transfused (after each chemotherapy cycle).
- Occurrence of adverse event (at each visit).
- Evaluation of vital signs.
- ECOG performance score.
- **Quality of Life questionnaire: Cancer Linear Analogue Scale after 4 or 6 (3weekly cycles) 8 or 9 and 12 weeks of epoetin alfa treatment. FACT An, after 8 or 9 and 12 weeks.**

Subjects should be unaware of any of the haematology results prior to completion of the questionaires.

STUDY COMPLETION

The last formal study visit is scheduled after completion of 12 weeks. If the investigator and subject agree then study medication may be continued beyond this point. Treatment with epoetin alfa may continue until 4 weeks after the end of chemotherapy. A limited amount of additional information will then be collected at this follow-up visit, see below.

The following procedures will be performed after completion of 12 weeks:

- Physical examination including vital signs measurements, and any current clinical signs and symptoms of malignant disease.
- Tumour response to chemotherapy.
- Transfusion information, including Hb level prior to transfusion, units and type of product transfused.
- Possible occurrence of adverse events.
- ECOG performance score, as determined by the investigator.
- Quality of Life questionnaires: FACT An and Cancer Linear Analogue Scale, as completed by subject.

Subjects should be unaware of any of the haematology results prior to completion of the questionnaires.

FOLLOW UP

For subjects who wish to continue on epoetin alfa therapy beyond 12 weeks, a final follow up visit will be scheduled. Treatment with epoetin alfa may continue for 4 weeks after the end of chemotherapy up to a maximum of 28 weeks total treatment. The following information will be collected at this visit

- Hemoglobin at the end of treatment.
- Number of chemotherapy cycles completed in total and with concurrent epoetin alfa
- Details of epoetin dosing (final dose and date).
- Tumour outcome assessment
- Serious adverse events (as this is an optional follow up period only sreiou adverse events must be reported).

DISCONTINUATION OF CHEMOTHERAPY

If chemotherapy is discontinued, the subject may continue on Epoetin alfa therapy until 4 weeks after the end of chemotherapy. At the time chemotherapy is discontinued, the following evaluations must be completed.

- Clinical laboratory tests: Hemoglobin.
- Tumour response to chemotherapy. Longer term (up to 6 months) follow up may be implemented, but will not require further study visits.

STUDY EVALUATIONS

Primary parameter

The primary efficacy parameter will be the improvement in quality of life, measured by decrease in FACT-AN scores from baseline. This will be analysed for all patients who have completed at least 8 weeks of treatment. The FACT-An will be administered at entry, after 8 or 9 weeks and finally after 12 weeks.

The complete quality of life battery, composed of the FACT-An and the Cancer Linear Analogue Scale, is self-administered by the subject and addresses issues of functioning, well-being and specific fatigue experiences. The questionnaires should always be completed in the same order, i.e., starting with the FACT-An,

then the Cancer Linear Analogue Scale. Subjects should be unaware of any of the haematology results prior to completion of the questionnaires.

Secondary parameters

Secondary parameters include the following

HAEMATOLOGICAL RESPONSE

A Complete haematological response is defined as an increase in hemoglobin of 2.0g/dl or more from baseline. Patients who achieve a hemoglobin level >14.0 g/dl at any time during treatment will also be regarded as having demonstrated a complete response.

A partial haematological response, will be defined as an increase in hemoglobin of 1-1.99 g/dL from baseline, whilst a holding response, will be defined as an increase in hemoglobin of up to 0.99 g/dL from baseline baseline combined with an increase in reticulocytes of > 40,000/μl.

Treatment failures are non-responders, defined as either no change or a fall in hemoglobin level, from baseline accompanied by an increase in reticulocytes < 40,000/μl. Non-responders will also include those with a hemoglobin increase that have received blood transfusion within the preceding four weeks.

QUALITY OF LIFE (CLAS)

Quality of life, Energy levels and activity as measured by the Cancer Linear Analogue Scale (CLAS) will be recorded at each study visit.

ECOG PERFORMANCE SCORE

ECOG performance status will be assessed at each study visit.

TUMOUR RESPONSE TO CHEMOTHERAPY.

Tumour response to chemotherapy will be assessed at 12 weeks and after any follow up period.

Other assessments

INCIDENCE OF BLOOD TRANSFUSIONS

The number of allogenic blood transfusions will be recorded for all patients during the treatment period.

PRE-EMINENT QUALITY OF LIFE CONCERN

As an additional evaluation subjects will be asked to indicate which item from the FACT-AN 'additional concerns' section is of greatest importance to them. This will be recorded in the CRF and a subject to separate analysis. The aim of this is to identify what items are most important to subjects, and to investigate any correlation between the responses to the individual item selected, and the complete scale.

Safety Evaluations

The following safety evaluations will be performed during the study to measure the safety and tolerability of Epoetin alfa

Adverse Events (AEs): AEs will be reported by the subject (or where appropriate by the subject's legally authorized representative) for the duration of the study. AEs will be followed by the investigator to satisfactory resolution, including those persisting beyond the end of the study. Further details on AE reporting are provided in the next section.

Clinical laboratory tests as follows:

Hematology Panel

- - hemoglobin
- - haematocrit
- - reticulocyte count (μL^{-1})

Vital Signs

Any abnormalities persisting at the end of the study will be followed until resolution, or until reaching a clinically stable endpoint.

Withdrawal

Subject participation may be terminated prior to completing the study (12 weeks) for any of the following reasons:

- Adverse Event
- Subject choice
- Lost to follow-up
- Other

Subjects who withdraw should have the procedure performed as prescribed for the Study Termination visit.

Additionally, the investigator is to retrieve all remaining study drug containers, whether empty or containing drug.

When a subject withdraws prior to completing the study, the reason for withdrawal is to be documented on the CRFs and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced.

STATISTICAL METHODS

The analysis of the data will be the responsibility of Janssen-Cilag, European Medical Affairs and will be carried out by the Data Management & Statistics Unit of DR Dimensione Ricerca (Rome).

In this chapter only the most important aspects of the statistical analysis are described. These sections were copied from the corresponding sections of the detailed statistical analysis plan (SAP) which has been written and authorized at the same time as this protocol. The SAP is an official internal Janssen-Cilag, European Medical Affairs document and is available on request only.

Study Population

The number of subjects, who were enrolled, and treated and who completed each visit (± allowed time frame) of study will be tabulated by center and country as well as overall/combined. Furthermore, a graphical presentation of the disposition of subjects by center and country will be given.

PROTOCOL VIOLATIONS

All protocol violations will be determined by medical, clinical and biometrics personnel and will be reported by center and country.

SUBJECTS DATA SETS

All-subject-Treated Group (AST)

The All-Subjects-Treated (AST) group consists of all subjects, who received at least one dose of in-treatment study medication. In cases where all dispensed study medication was returned (per investigator's record), the subject will be considered as non-treated, and will be excluded from the AST-group.

Intent to Treat Group (ITT)

The Intent to Treat Group (ITT) group consists of all subjects from the AST-group, who had at least one post-baseline assessment of the primary variable.

Per Protocol Group (PP)

The Per Protocol Group (PP) group consists of all subjects from the ITT-group, without any major protocol violation.

Efficacy Evaluations

PLANNED ANALYSES

All efficacy and safety parameters will be presented descriptively. Tables of descriptive statistical parameters (number of non-missing values, mean, standard deviation, median, range) and/or frequency tables (number of non-missing values, percentage) will be constructed for each time point.

Primary Efficacy Parameter

The main objective of this study will be change of Quality of life from baseline to end of treatment in all subjects who complete 8/9 weeks or more according to the FACT (Functional Assessment of Chronic Illness Therapy) - Anemia Total Score.

Paired Sample T test will be used to test if two related samples come from populations with the same mean. In this case the two population will be the subjects before (baseline) and after the treatment period.

The Functional Assessment of Chronic Illness Therapy Anemia scale is multilingual validated scale composed of three scales:

- Fact-G
- Fact-F
- Fact-non F

The FACT scales are designed for patient self-administration, but can also be administered by interview format. For self-administration, subjects should be instructed to read the brief directions at the top of the page. After the subject's correct understanding has been confirmed, he/she should be encouraged to complete every item in order without skipping any. Some subjects may feel that a given question is not applicable to them, and will therefore skip the item all-together. **Subjects should be encouraged to circle the response that is most applicable.**

SCORING THE SCALES

In the FACT-G negatively stated items are reversed by subtracting the response from "4". After reversing proper items, all subscale items are summed to total, which is the subscale score.

Handling missing data: If there are missing items, subscale scores can be prorated. This is done by multiplying the sum of subscale by the number of items in the subscale, then dividing by the number of items actually answered. This can be done using the formula below:

$$\frac{\sum a_i \times N}{n}$$

where a_i is an item score, N the number of items in the subscale and n the number of items answered. When there are missing data, prorating by subscale in this way is acceptable as long as **more than** 50% of the items were answered (i.e., a minimum of 4 of 7 items, 4 of 6 items, etc.). The total score is then calculated as the sum of the unweighted subscale score.

The FACT scale is considered to be an acceptable indicator of patient quality of life as long as overall item response rate is **greater than** 80% (i.e., at least 22 of 27 FACT-G items completed). This is not to be confused with individual subscale item response rate, which allows a subscale score to be prorated for missing items if greater than 50% of items are answered.

Scoring specific scale: The total score for the Fact-An scale is the sum of the FACT-G (the first subscales common to almost all scales) plus the "Additional concern" subscale. In the Fact-An the "Additional concern" are composed of two subscale, the Fatigue items and non-Fatigue items which together are the Anemia items. Again, over 50% must be completed in order to consider the subscale score valid.

Secondary Efficacy Parameter

Secondary efficacy parameters are will be defined as follow:

a. Change in the total fatigue subscale score between end of trial and baseline;

b. Change in the total non-fatigue subscale score between end of trial and baseline;

c. Change in the total anemia subscale score between end of trial and baseline;

d. Change in the FACT fatigue total score between end of trial and baseline;

e. Change in the VAS between end of trial and baseline;

f. Change in the Hemoglobin values between baseline and different visits.

Point from a to d will be also analyzed into different class of hemoglobin value (9-10.5, 10.5-11, 11-12 g/dl). The Pearson's correlation coefficient will be used to quantify the strength of the linear relationship between the two variables. Point e will be evaluated using a paired t-test. Point f will be evaluated using repeated measures statistics. Other data explorations will be made.

Other assessments

Incidence of allogenic blood transfusion will be tabulated and presented in relation to hemoglobin level, tumour type and staging.

The quality of life item identified by the subject as being of most importance will be tabulated for all patients. A comparison will be made between responses to this item and the complete FACT-An.

Safety Evaluations

All individual values will be listed. Vital sign parameters will be assessed by means of descriptive statistical analysis. Laboratory values will be compared to their reference ranges. The product specific WHO-ARD (World Health Organisation Adverse Reaction Dictionary) will be used for the coding of all adverse events reported. In addition, adverse events will be tabulated according to severity and will be categorised by event, body system and preferred term.

SAMPLE SIZE DETERMINATION

A total of 1000 patients are judged to be an appropriate number to evaluate quality of life as defined by the protocol. This number is also suitable to evaluate the possible effects on tumour response to chemotherapy. As this is

a non-comparative trial, no formal power calculation will be made. The protocol contains novel and exploratory elements, in particular a definition of early intervention based on a hemoglobin entry criteria of 12.0 g/dl. Because of this it is not practical to construct a power calculation based on existing data

INTERIM ANALYSIS

No interim analyses are planned.

STUDY DRUG INFORMATION

Physical Description of Study Drug(s)

Epoetin alfa is a sterile, clear, colourless aqueous solution for injection, which will be provided in pre-filled, single-use syringes containing 10,000 IU/mL Epoetin alfa (a recombinant human erythropoietin) and 2.5 mg/mL human serum albumin in 1 mL of phosphate buffer. The activity of Epoetin alfa is determined by comparison of the product to the World Health Organisation (WHO) International Reference Standard #2 (10 IU/mL) by both bioassay and radioimmunoassay (RIA).

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WHAT IS CLAIMED IS:

1. A method for treatment of a subject having a malignancy, comprising the steps, in any order or concurrently:

a) administering a therapeutically effective amount of an anti-tumor agent; and

b) administering a therapeutically effective amount of erythropoietin,

wherein said subject is non-anemic.

2. The method of claim 1 wherein the anti-tumor agent is at least one agent selected from a group consisting of cisplatin, cis-dichlorodiamineplatinum, cyclophosphamide, fluorouracil, epirubicin, methotrexate, vincristine, doxorubicin, bleomycin, or etoposide.

3. The method of claim 1 wherein the malignancy is selected from a group consisting of solid tumors, hematological tumors, sarcomas, carcinomas, neoplasms, Non-hodgkins lymphoma, myeloma, Hodgkin's lymphoma, leukemia, colon, rectal, colorectal, stomach, gastrointestinal, ovarian, lung, pancreas, breast, and prostate.

4. A method for treatment of an anemic subject having a malignancy, comprising:

a) administering a therapeutically effective amount of an antitumor agent; and

b) administering a therapeutically effective amount of erythropoietin prior to or beginning with the first administration of the antitumor agent.

5. The method of claim 4 wherein the anti-tumor agent is at least one agent selected from the group consisting of cisplatin, cis-dichlorodiamineplatinum, cyclophosphamide, fluorouracil, epirubicin, methotrexate, vincristine, doxorubicin, bleomycin, or etoposide.

6. The method of claim 4 wherein the malignancy is selected from the group consisting of solid tumors, hematological tumors, sarcomas, carcinomas, neoplasms, Non-hodgkins lymphoma, myeloma, Hodgkin's lymphoma, leukemia, colon, rectal, colorectal, stomach, gastrointestinal, ovarian, lung, pancreas, breast, and prostate.

7. A method for the treatment of a non-anemic subject having malignancies, comprising the steps, in any order or concurrently:

a) administering a therapeutically effective amount of an antitumor agent; and

b) administering a therapeutically effective amount of erythropoietin,

wherein said treatment improves physical performance and well being of said subject.

8. The method of claim 7 wherein the anti-tumor agent is at least one agent selected from the group consisting of cisplatin, cis-dichlorodiamineplatinum, cyclophosphamide, fluorouracil, epirubicin, methotrexate, vincristine, doxorubicin, bleomycin, or etoposide.

9. The method of claim 7 wherein the malignancy is selected from the group consisting of solid tumors, hematological tumors, sarcomas, carcinomas, neoplasms, Non-hodgkins lymphoma, myeloma, Hodgkin's lymphoma, leukemia, colon, rectal, colorectal, stomach, gastrointestinal, ovarian, lung, pancreas, breast, and prostate.

10. A method for the treatment of an anemic or non-anemic subject having malignancies, comprising the steps, in any order or concurrently:

a) administering a therapeutically effective amount of an antitumor agent; and

b) administering a therapeutically effective amount of erythropoietin,

wherein said treatment prevents a decrease in physical performance and well being of said subject.

11. The method of claim 10 wherein the anti-tumor agent is at least one agent selected from the group consisting of cisplatin, cis-dichlorodiamineplatinum, cyclophosphamide, fluorouracil, epirubicin, methotrexate, vincristine, doxorubicin, bleomycin, or etoposide.

12. The method of claim 10 wherein the malignancy is selected from the group consisting of solid tumors, hematological tumors, sarcomas, carcinomas, neoplasms, Non-hodgkins lymphoma, myeloma, Hodgkin's lymphoma, leukemia, colon, rectal, colorectal, stomach, gastrointestinal, ovarian, lung, pancreas, breast, and prostate.

13. A method for treatment of an anemic and non-anemic subject having malignancies, comprising the steps, in any order or concurrently:

a) administering a therapeutically effective amount of an antitumor agent; and

b) administering a therapeutically effective amount of erythropoietin,

wherein said treatment increases survival of said subject post-treatment with the antitumor agent.

14. The method of claim 13 wherein the anti-tumor agent is at least one agent selected from the group consisting of cisplatin, cis-dichlorodiamineplatinum, cyclophosphamide, fluorouracil, epirubicin, methotrexate, vincristine, doxorubicin, bleomycin, or etoposide.

15. A method for treatment of a subject having breast cancer, comprising the steps, in any order or concurrently:

a) administering a therapeutically effective amount of an antitumor agent; and

b) administering a therapeutically effective amount of erythropoietin,

wherein said treatment increases survival of said subject.

16. A method for treatment of a subject having myeloma, comprising the steps, in any order or concurrently:

a) administering a therapeutically effective amount of an antitumor agent; and

b) administering a therapeutically effective amount of erythropoietin,

wherein said treatment increases survival of said subject.

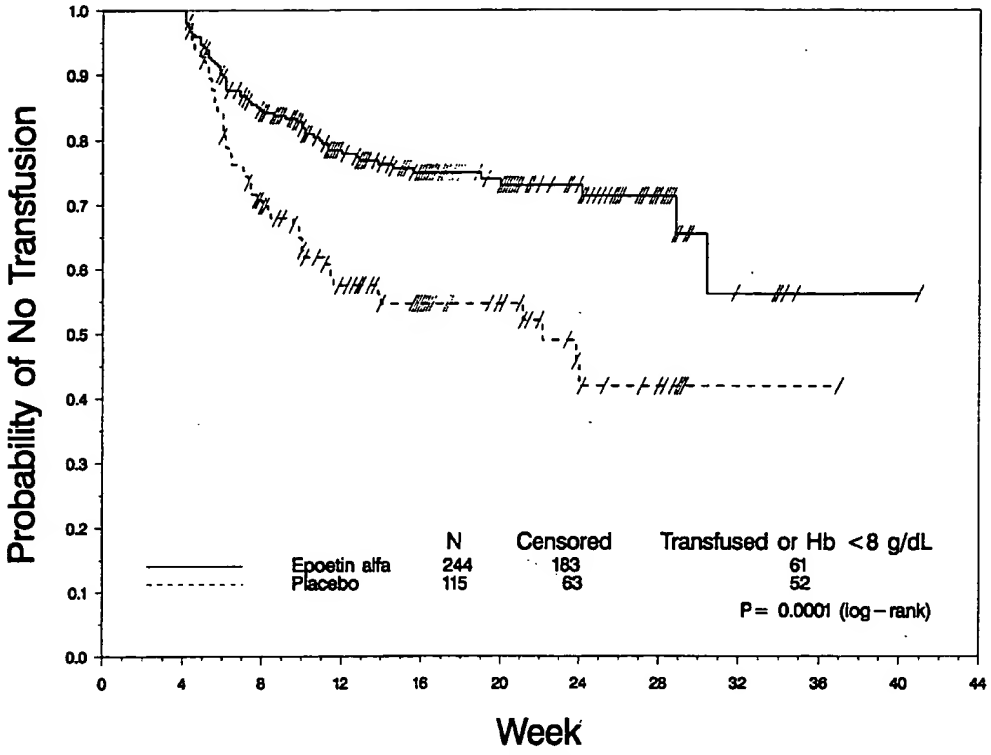
17. A method for treatment of a subject having ovarian cancer, comprising the steps, in any order or concurrently:

a) administering a therapeutically effective amount of an antitumor agent; and

b) administering a therapeutically effective amount of erythropoietin,

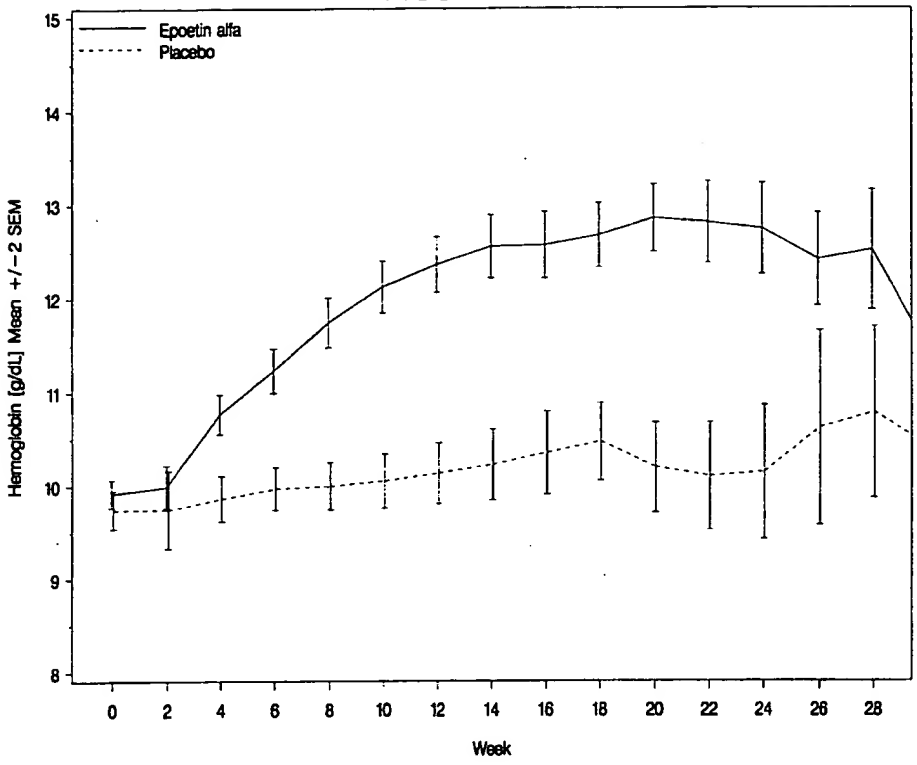
wherein said treatment increases survival of said subject.

FIGURE 1



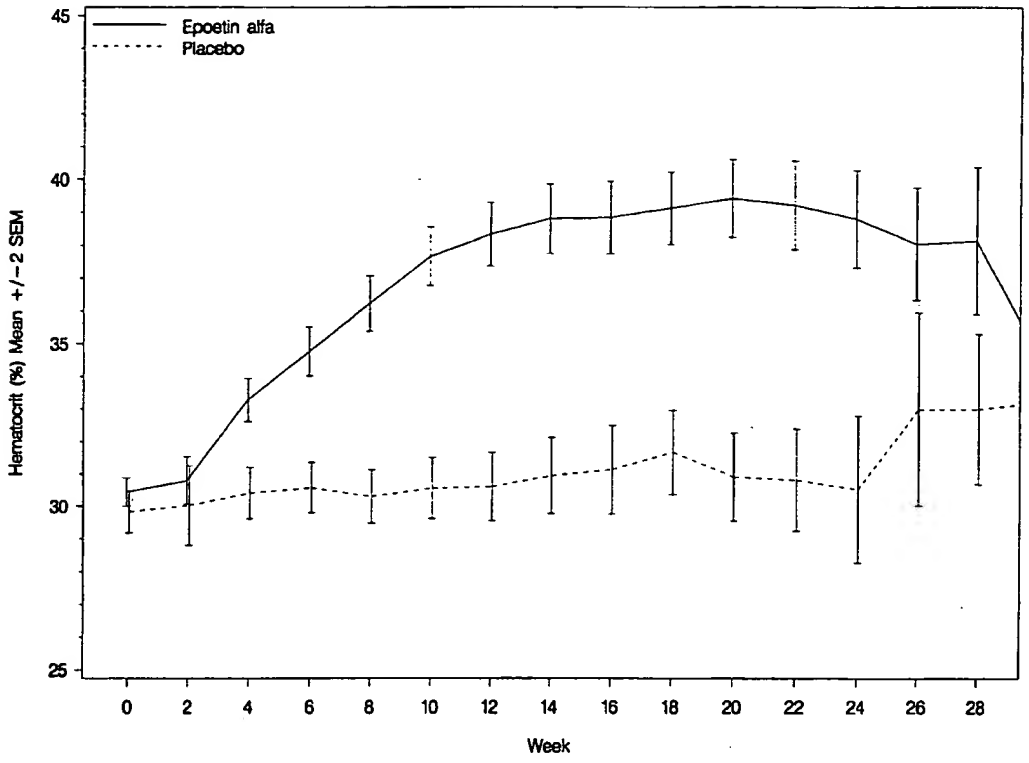
NOTE: Slashes represent censored observations, i.e., the end of the observation period for subjects who were not transfused.

FIGURE 2



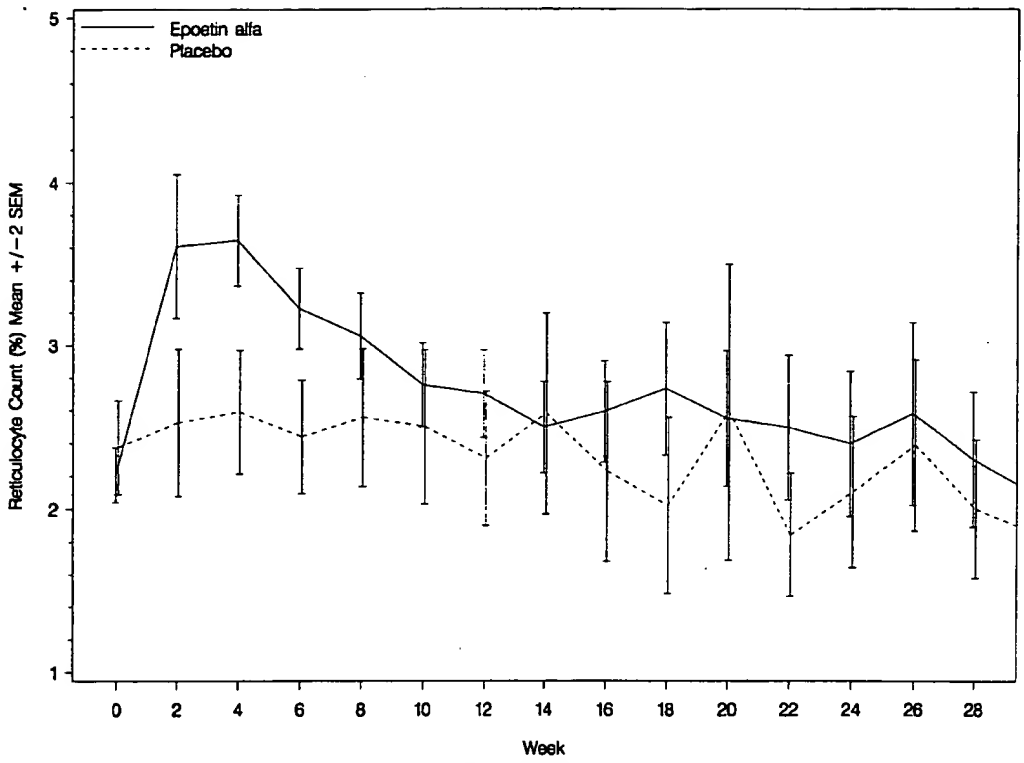
Note: Weeks calculated as study day/7. Missing values on study are substituted by previous observation.

FIGURE 3



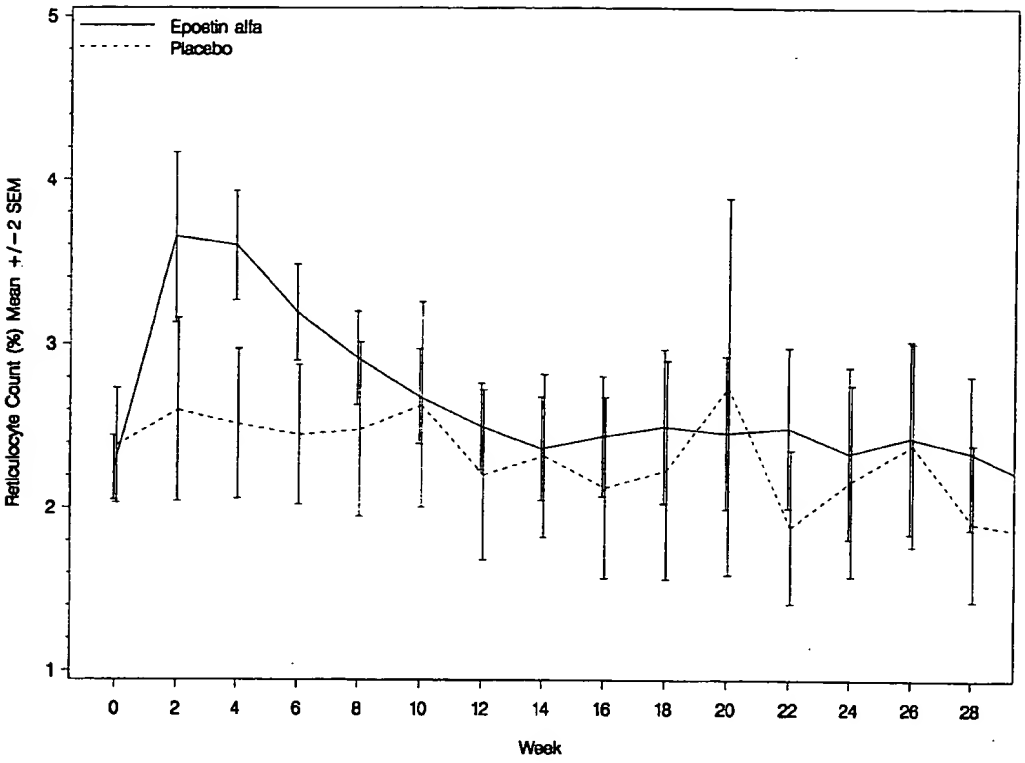
Note: Weeks calculated as study day/7. Missing values on study are substituted by previous observation.

FIGURE 4



Note: Weeks calculated as study day/7. Missing values on study are substituted by previous observation.

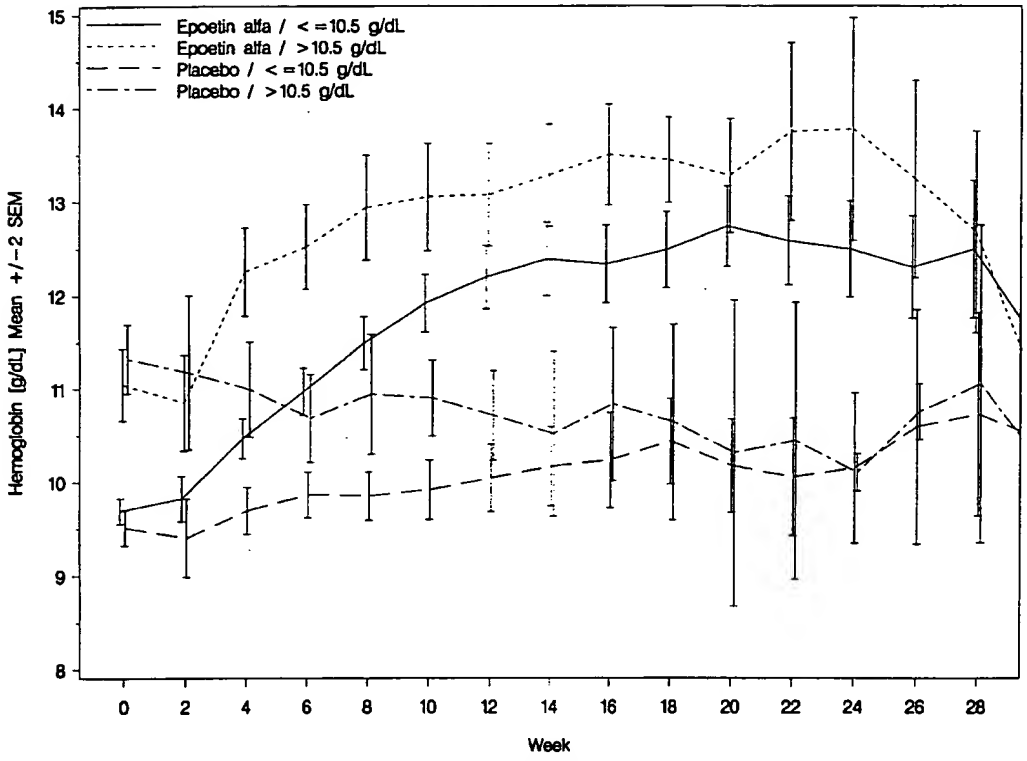
FIGURE 5



Note: Weeks calculated as study day/7. Missing values on study are substituted by previous observation.

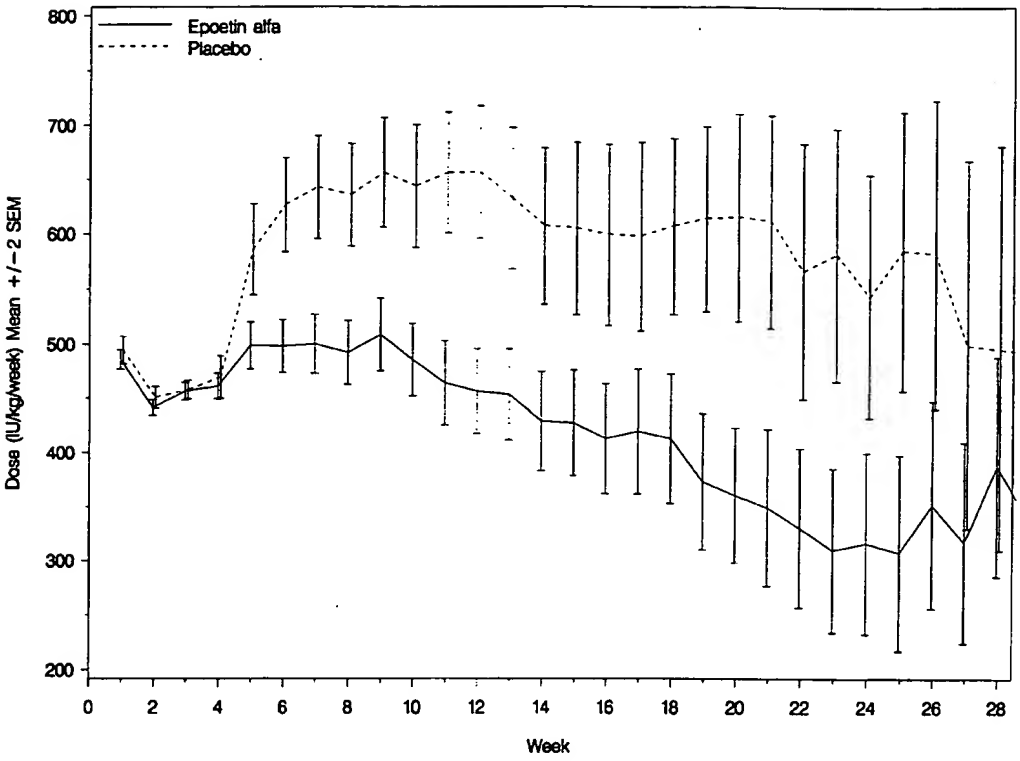
5

FIGURE 6



NOTE: Weeks calculated as study day/7. Missing values on-study are substituted with previous observation.

FIGURE 7



Note: Week calculated from the day of study drug administration. Incomplete last weeks omitted

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/12864

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 37/10
US CL :514/8

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/8

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	US 5,922,674 A (ANAGNOSTOU ET AL) 13 July 1999 (13/7/99), see entire document.	1-17
A	US 4,745,099 A (AKAMATSU ET AL) 17 May 1988 (17/5/98), see entire document.	1-3
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Y		4-17

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 23 JUNE 2000	Date of mailing of the international search report 12 JUL 2000
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